VOLUME 78 • JULY 1958 • NUMBER 1

A.M.A. ARCHIVES OF

DERMATOLOGY

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Polyethylene Squeeze Bottles for Potassium Hydroxide Solutions
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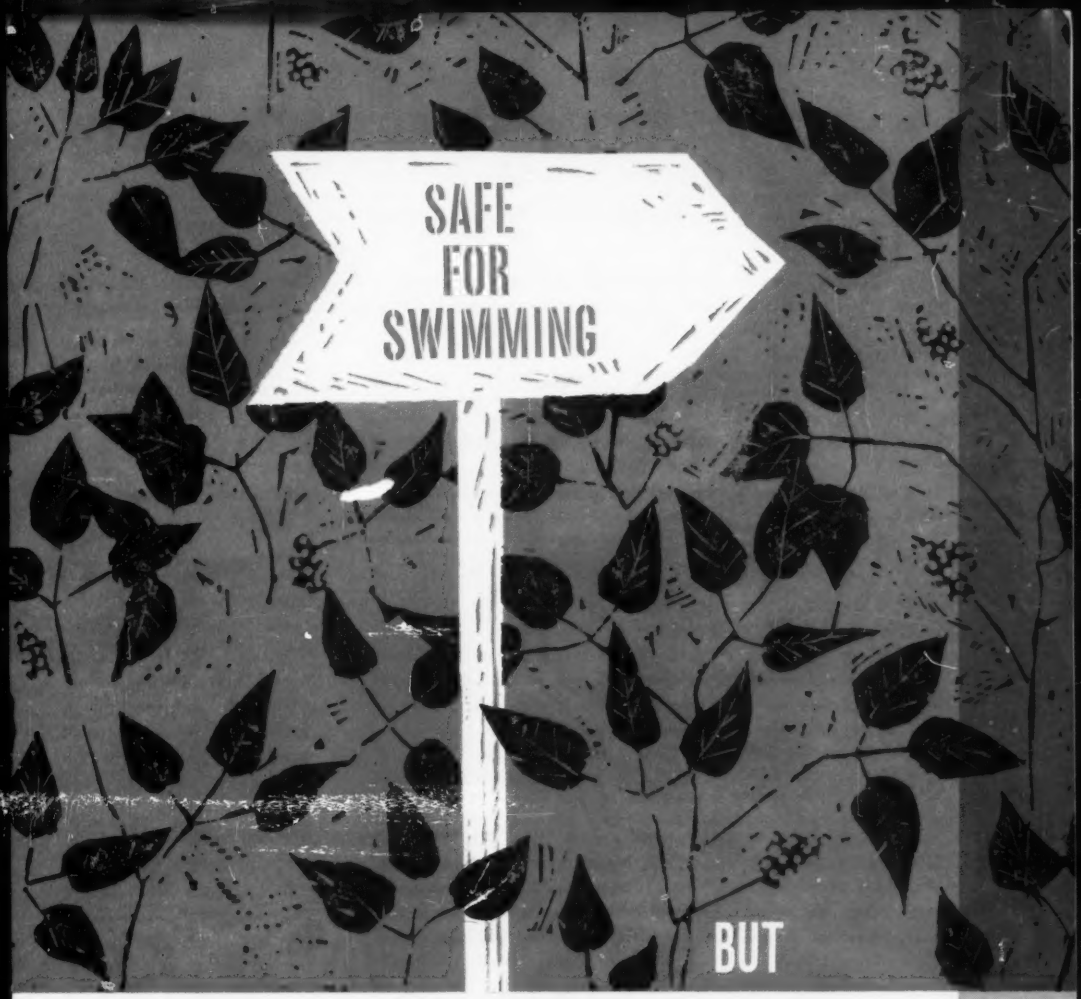

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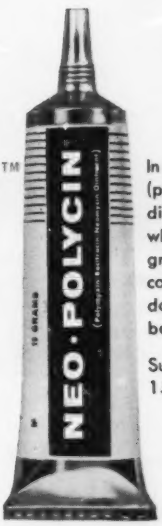

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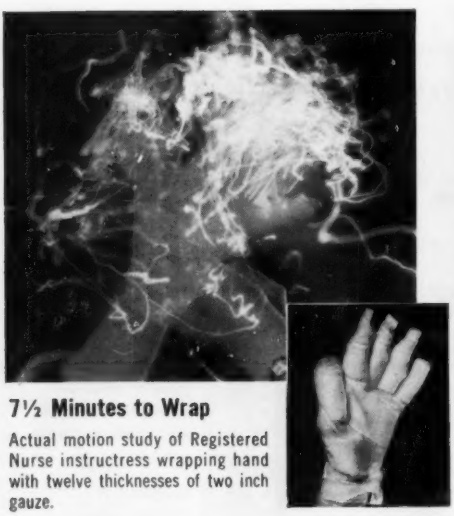

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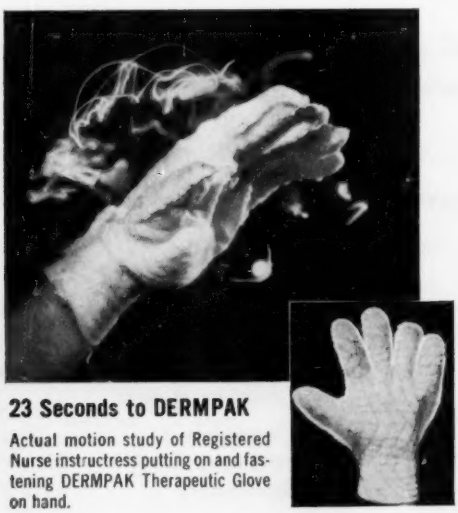

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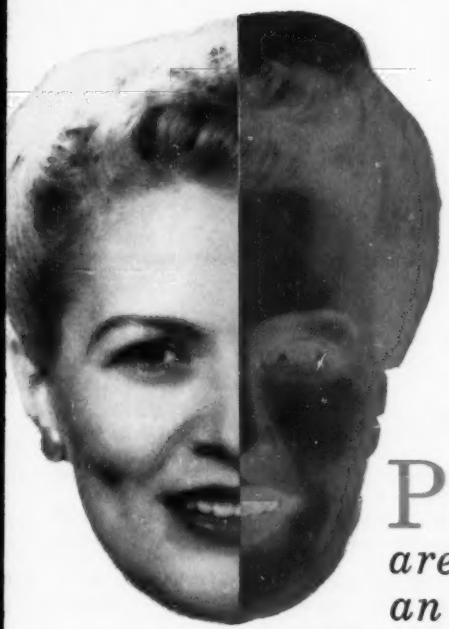

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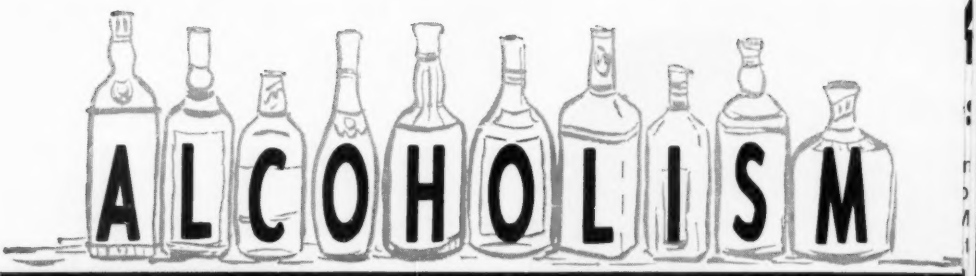

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1. Colavincenzo, J. W., and others: Pennsylvania M. J. *59*:338 (March) 1956.
2. Ansbro, F. P., and Furlong, R. E.: Adelphi Hosp. Bull. *15*:2 (May) 1957.
3. Foldes, F. F., and McNall, P. G.: Anesthesiology *13*:287 (May) 1952.

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1. Wiener, K.: Systemic Associations and Treatment of Skin Diseases, St. Louis, The C. V. Mosby Company, 1955, pp. 329; 458-459.
2. Perry, D. J.; Mount, G. D., and Browne, B. W.: The Effect of Varying Oral Dosages of Banthīne, Pro-Banthīne and Prantal on the Galvanic Skin Response, J. Invest. Dermat. *28*:239 (March) 1957.
3. Olansky, S., and Callaway, J. L., in Modern Medicine 1958 Annual (Part 1): Management of Superficial Infections, Minneapolis, Modern Medicine, 1957, p. 46.

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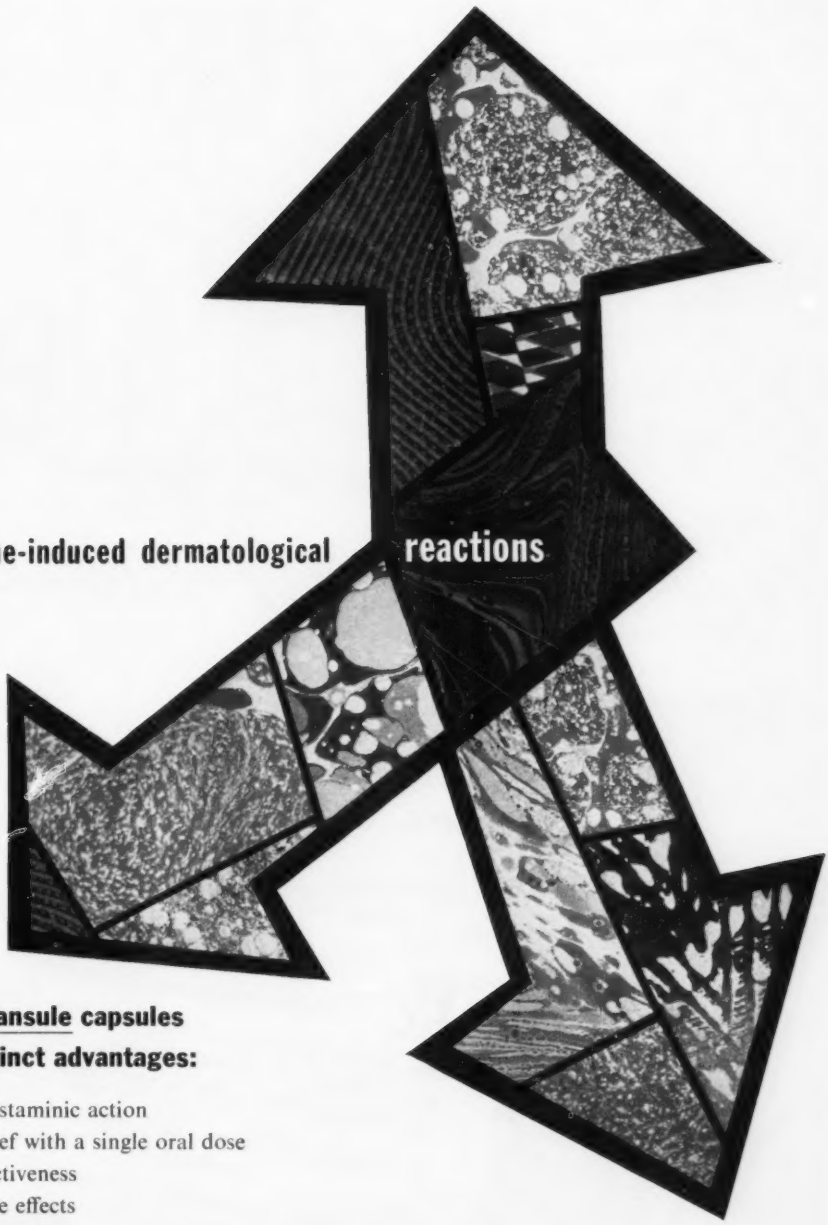

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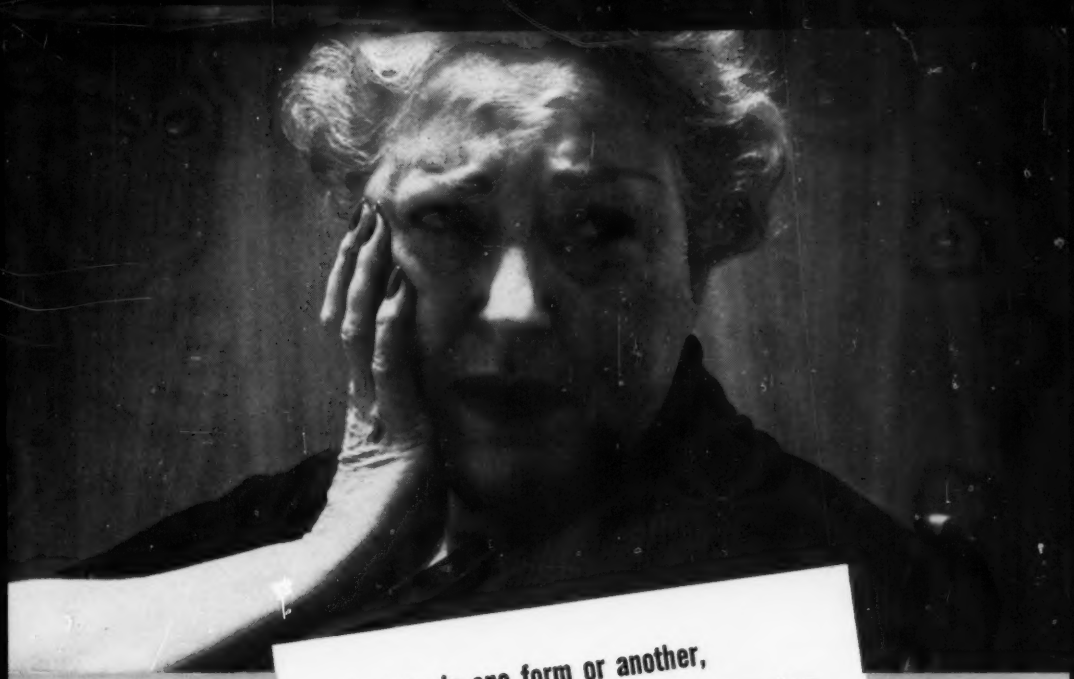

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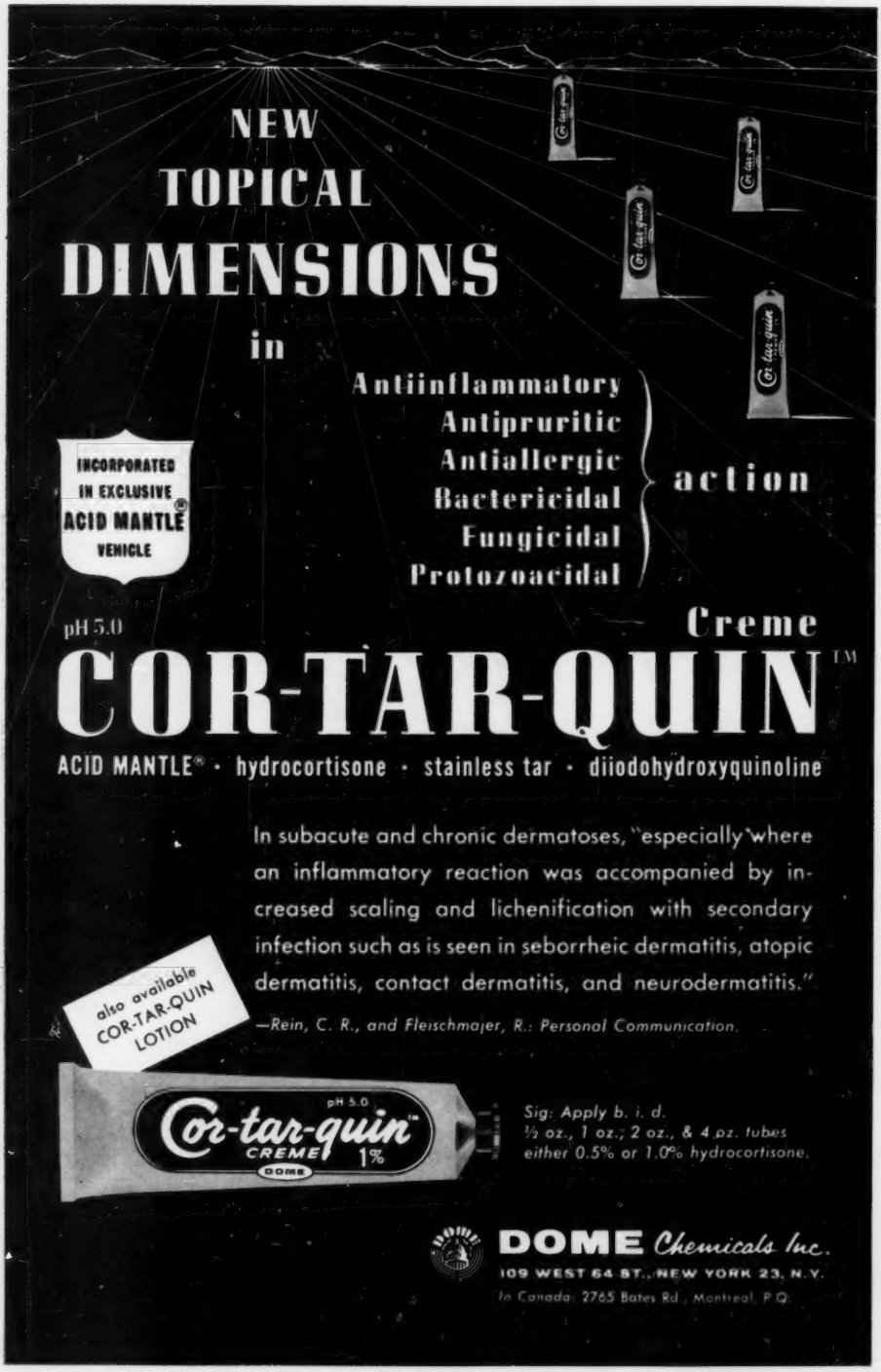
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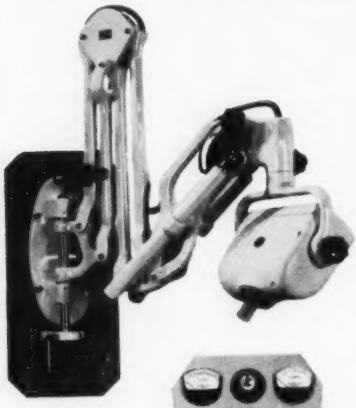

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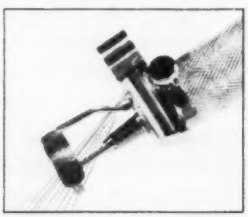

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1. McCarthy, John T., and Nelson, Carl T.: Pediatric Clinics of North America, Philadelphia, W. B. Saunders & Co., August 1956, p. 514.
2. Samuels, Saul S.: Angiology 7:532 (Dec.) 1956.
3. Panaccio, Victor: Canad. M. A. J. 75:592 (Oct.) 1956.

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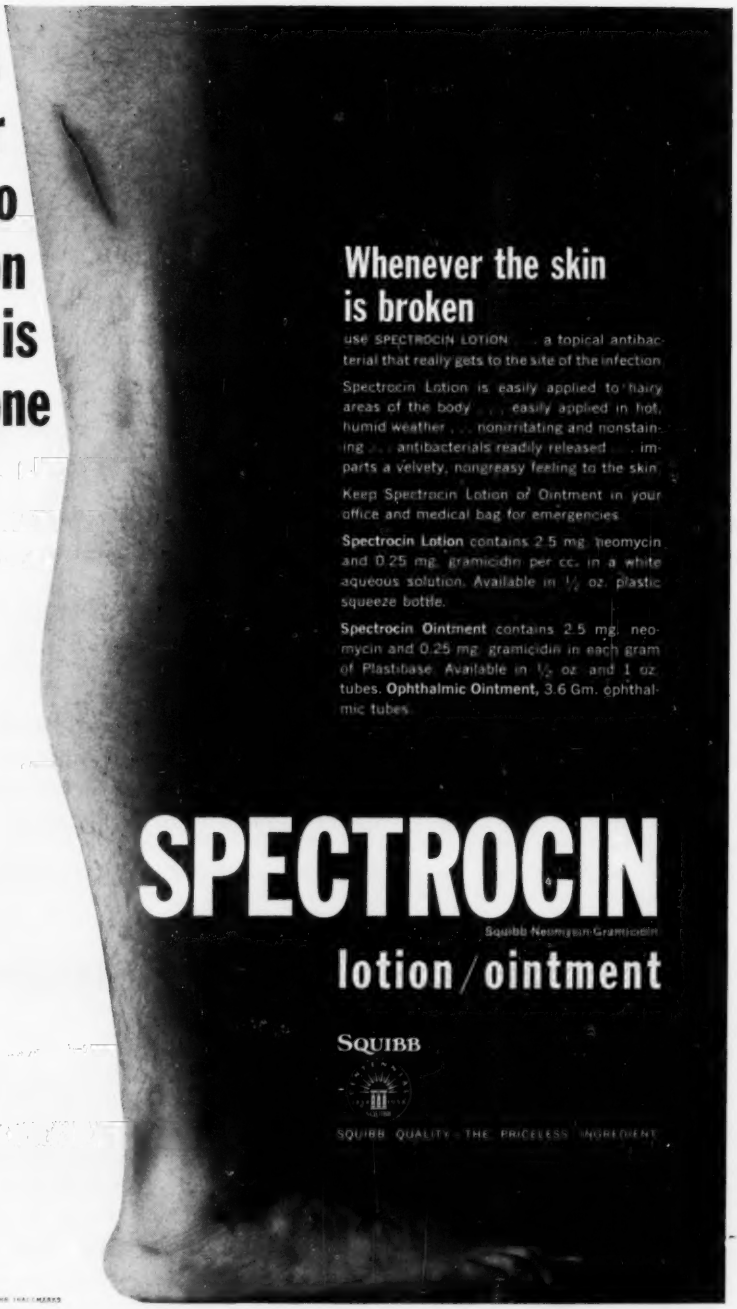

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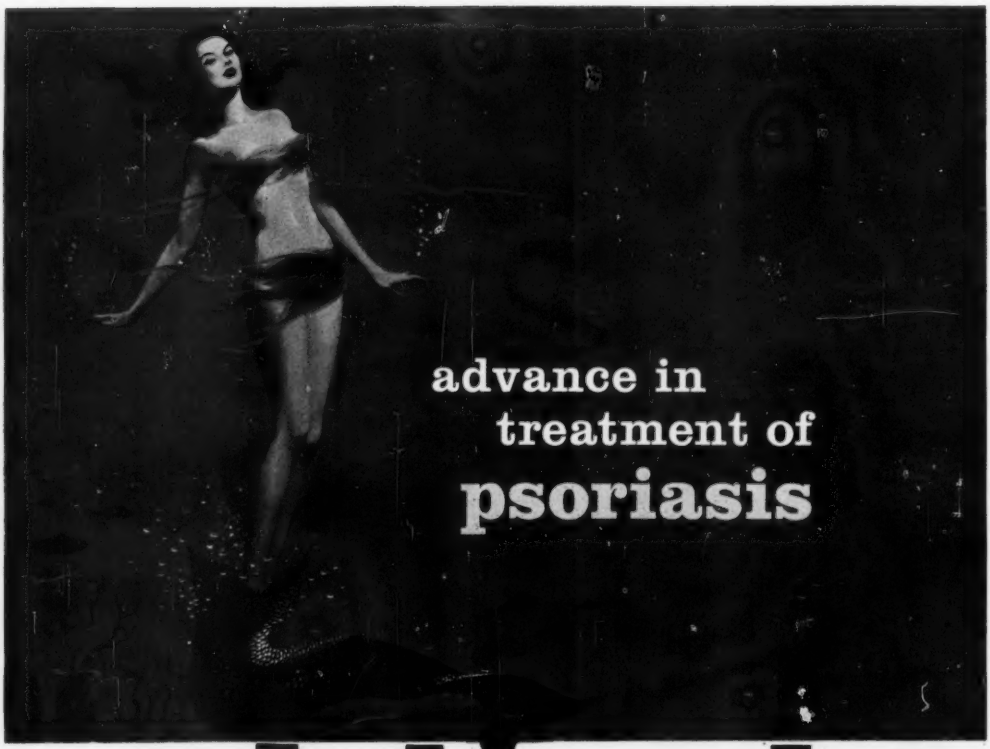

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A.M.A. ARCHIVES OF
DERMATOLOGY

Dermatology's Debt to Dermatohistopathology

CLARK W. FINNERUD, M.D., Chicago

Dermatologists owe a great debt to those in their ranks who initiated and pursued the microscopic study of skin diseases.

All phases of knowledge about skin diseases have greatly advanced and kept pace with the progress of medicine, but "lest we forget" I should like to review the development of the science of dermatopathology, pay tribute to some of its founders and to those who have contributed so much to elevate the microscopic evaluation of dermatoses, illustrate some of the more important specific accomplishments, and appraise the indebtedness.

Historically, the development of our knowledge of dermatohistopathology may be considered to have begun with the discovery of the microscope, although naming a single point in time is an arbitrary matter, history being a continuum. Thus, one might say that dermatopathology began with the Greeks, when Hippocrates, in 450 B. C., declared that disease arose from natural causes and not from the anger of the gods.

The old statement that a "dermatologist should be an internist who knows the skin" remains a time-proven maxim. Similarly, one might claim that a dermatopathologist of dermatohistopathologist should be a pathologist who knows the skin. However, there now exist many good cutaneous histopathologists who are not particularly well versed in general pathology, our late friend Dr. Frederick D. Weidman being a notable exception. On the other hand, there are, at least in this country, almost no general pathologists who are expert on dermatopathology. Dermatohistopathology, therefore, might be considered a specialty within a specialty and the private property of dermatologists.

I request your indulgence in allowing me to interject my personal problem of about 40 years ago, which illustrates some of the points I wish to emphasize.

While working in the Cook County Morgue from 1916 to 1918, performing autopsies and also assisting in the teaching of general pathology, I was fortunate in being associated with some distinguished teachers of that branch of medical science. Although at that time I had not considered specializing in dermatology, it always having been my ambition to be a pathologist or a surgeon, I became deeply impressed by the fact that these experts in general pathology knew virtually nothing about cutaneous histopathology, aside from their ability to diagnose chiefly the tumors. Indeed, even today, 40 years later, as mentioned, it is decidedly the exception to find a general pathologist who is versed in general cutaneous histopathology.

Because of a combination of circumstances, I soon after began the study of dermatology, and, probably because of this earlier exposure to general pathology, the

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Presidential Address. Read before the 78th Annual Meeting of the American Dermatological Association, Inc., Sun Valley, Idaho, June 4, 1958.

microscopic aspect of dermatology seemed as important and interesting to me as its clinical side. But the problem I then confronted was where to obtain such histologic training.

Originally, dermatologists learned their fundamentals of dermal pathology from the great Viennese and German students and teachers of general pathology of the last half of the 19th century, from such renowned men as Virchow, Auspitz, and Rokitansky. But in the United States at that time, and in fact up to about the early thirties, scant attention was paid to this branch of our specialty; there were only Pollitzer, Satenstein and Highman, in New York, who had achieved some reputation as dermatohistopathologists, and later Fred Weidman. So, off I went to Vienna in 1924 to study under Kren, Kyrle, and Artz, with a letter of introduction to Professor Kren from Dr. Henry Michelson. Frances Pascher has stated, in a review of the history of the New York Skin and Cancer Unit, that it was only in 1934 that students no longer felt compelled to go to such dermatologic centers as those of Vienna or Hamburg or Zurich. Astounding, is it not, that, in the span of the average professional lifetime of a dermatologist, knowledge of dermal histopathology has progressed from virtual nonexistence to its present status?

Up until about 1930, at the meetings of the various local dermatological societies in the United States, commonly all patients were presented without a single accompanying microscopic slide. Today the reverse is true. In recent years microscopic sections have accompanied about 90% of the patients presented before the Chicago Dermatological Society. In 1956 Pillsbury stated that, in his own clinic, biopsy examination is now undertaken with at least 10 times the frequency of 15 years ago. I find that is about the average in most of our large clinics.

In communications from the heads of dermatohistopathology in 13 of the leading institutions in the United States, I have learned that in recent years an average of nearly 3000 skin biopsy specimens are run through and studied annually per institution, including those from private cases. These figures include an approximation of 10,000 specimens annually examined by the Armed Forces Institute of Pathology. Even if we omit that great institution, so great that it might be considered unfair to include it, from the tabulation, we arrive at an annual average total of over 2300 specimens per institution, or nearly 200 per month. In our private office, taking only specimens necessary for diagnosis and for medicolegal reasons, we average about 200 biopsies per year, a figure approximating that of a number of my colleagues to whom I have addressed inquiry. All of these figures emphasize the tremendous importance now attached to dermatohistopathologic study, an acknowledgement of our debt.

Another way of acknowledging our debt is to call the roll of the great men whose debtors we are. I should like, if it were only possible in a short paper, to name all those contributing to the development of anatomy, of pathology, of histology, of dermatology—to name all those participating in the development of lenses, microscopes, microtomes, dyes, and all the other allied sciences and inventions and discoveries that were the precursors of our subspecialty. But, since that would take much time, we can only pay our respects to some of the great historical figures.

For anatomy, let us name Galen, da Vinci, Vesalius. For lens making, Bourne, Porta, Manzini; for microscopes, d'Orleans, Hooke, Jansen. And we might list for microtomes, Valentin, Ranvier, Minot; for embedding procedures, Heidenhain, Klebs, Duval; for staining, Gerlach, Böhmer, von Recklinghausen. These names have a certain rhythm and poetry, something like the "begat" series in the Bible. For histology, let us name Malpighi, Leeuwenhoek, and Bichat, who, although he did not use the microscope, was the first

to study tissues; for pathology, Malpighi, Morgagni, Bichat, Schleiden, Schwann, Rokitansky, Henle, Müller, Virchow. There are many others. But these names, these men, are the solid background.

And so, for dermatohistopathology, let us cite Stenson, Malpighi, Ruysch, Boerhaave, Cowper, Turner, Morgagni, Vater, Russi, and Astruc. I am trusting that these names will carry with them some of the importance of their place in history—these men were the earliest dermatohistopathologists, 1650 to 1750.

Then, the next arbitrary division in the rise of dermatohistopathology might be the period of 1750 to 1850. Here, among the French, we may list Bichat, Biett, Rayer, Alibert, Bazin, Cazenave, Gibert, Hardy, Devergie, Vidal, and Gruby. While representing the French school, which was renowned for its great contributions to *clinical* dermatology, as was the English school, these men were, nevertheless, among the first to recognize the potentialities of normal and pathologic histology; they were not solely "clinicians." However, it was the German-speaking scientists who contributed laboratory methods to the study of medicine. In Germany and Austria, among the pioneers of microscopic study of the skin, were Purkinje, Gurlt, Weber, Henle, Kolliker, Meissner, von Barensprung, Schönlein, Rosenbaum, and Gustave Simon, who wrote the first book describing the new microscopic and staining techniques of his day.

The development of microscopic anatomy proceeded slowly throughout the 18th century. Then, with the introduction of achromatic lenses and improved compound microscopes in the 1820's, the study of histology, both normal and pathologic, was made possible to an extent and accuracy hitherto undreamed of. But, in addition to these technical improvements, the time was favorable for major scientific developments, and the early part of the 19th centry saw more rapid progress. It was during this era that Schleiden and Schwann enunciated the cell theory; Virchow, proclaimed one of the greatest pathologists of all time, established the field of cellular pathology; Müller inaugurated modern physiology, and initial insight into the cell was gained from the investigations of Henle, von Mohl, Remak, and Purkinje. The greatest impetus to the development of modern histology was the formulating of the cell theory.

Karl Rokitansky, one of the greatest of all gross descriptive pathologists, was one of the chief founders of the New Vienna School, a school which derived from Morgagni and which was responsible for initiating the German-speaking scientists' leadership in world medicine. Rokitansky said that pathology, including the further development of histopathology, is the essential basis of physiopathology, the elementary doctrine for medical research, and the foundation of clinical knowledge.

Ferdinand von Hebra, the greatest dermatologist of the 19th century, was a representative of the New Vienna School at its height. It was he who applied Rokitansky's new pathology to the classification of skin diseases and, thus, was the creator of a sound dermatology based on pathologic anatomy. Hebra has also been called the founder of the histologic school of dermatology, although he was chiefly interested in clinical dermatology. Nevertheless, through his students, and through their students, and, in turn, through *their* students, it can be said that he was "father" to dermatohistopathology, as he was "father" or "master" to his students.

Some of Hebra's colleagues, disciples, students, and "descendants" are Tilbury and G. H. Fox, Duhring, Koebner, the Behrends, the Picks, Hans von Hebra, Neisser, von Neumann, the von Zeissls, Auspitz, Jarisch, Kaposi, the Jadassohns, the Riehls, Finger, Rille, Ehrmann, Simon, Erasmus Wilson, Lesser, Arndt, Arzt, Kerl, Nobl, Unna, von Zumbusch, Kren, Kumer, Kyrle, J. M. H. McLeod, Burchardt, Zuelzer, Lassar, J. Zeisler, Bloch, Hoffmann, Mulzer, F. and Hermann

Pinkus, Zinsser, Oscar Gans, and many, many others. Note among this roster the many great contributors to dermatohistopathology.

Let us name some of the other contributors, such as Weigert, who developed staining methods; Danielssen of Norway, who studied the histopathology of leprosy, and the Boecks, C. W. and his nephew, C. P. M., of tuberculid and sarcoid fame. Danielssen had noticed in 1848 that certain characteristic cells were found in leprous tissue; Armauer Hansen, in 1871, found small rods lying within the "lepra cells"; staining methods applied by Neisser and Hansen showed these rods to be bacilli; Unna, as early as 1885, tried to prove that these "leprosy cells" were not cells at all but were clumps of bacilli embedded in mucin and surrounded by atrophic connective tissue cells.

In France during this middle-to-late-19th-century period were Vidal, Leloir, Hardy, Besnier, Lailler, Brocq, Hallopeau, Darier, Sabouraud, and others. In England there were great clinicians, among them Crocker; Colcott Fox; Sir Malcom Morris; Galloway, Huxley, who described the membrane in the root of the human hair, and George Thin, who studied the histopathology of various skin diseases, among them Paget's disease of the nipple. For the United States, let me quote Pusey: "It is an interesting fact, generally unknown, that America can claim one important scientific contribution to the minute anatomy of the skin in the 18th century, although the work was done in London. This was the injection of the capillaries of the corium, and the demonstration of 'a fine vascular membrane immediately below the Malpighian layer of the skin, separate and distinct from the cutis and capable of separation from it through its whole extent'—the body of the corium and its superficial sub-papillary plexus of blood vessels." This was done by William Baynham (1749-1814), who was born in Virginia and trained in pathology in London.

It was Paul Gerson Unna, born in 1850 and died in 1929, who was the founder of dermatology as a branch of the exact natural sciences and the creator of modern dermatopathology and dermatotherapy. Unna, from the beginning of his career, tried to link together the clinical aspects, etiology, histology, and therapy of skin diseases. He wrote "Histopathology of Diseases of the Skin" (translated into English from the German by Norman Walker, 1896), a book requiring five years to write and based principally on his own work; in considering its value we should remember that only one book on dermatohistopathology had been previously published, that of Gustav Simon, in 1848. In the preface of his book, Unna wrote of the advantage which the dermatologist possesses in examining the skin: He can see the live object grossly before he excises the specimen; therefore, he may compare all details of clinical and histologic findings, and, because of this advantage, he has the responsibility for unceasing work until the macroscopic and the microscopic pathology come into harmony.

Unna invented new staining methods and discovered plasma cells, nevus cells, degenerative products of collagen and elastin, acanthosis, and spongiosis, ballooning and reticular degeneration in vesicular dermatoses. The chapter on nevi in his book will always remain a classic scientific contribution. In 1895 Unna demonstrated the streptobacillus of chancroid and established the value of the microscopic diagnosis of chancroid.

Unna did not neglect clinical dermatology in spite of his histopathologic zeal. He said that studies embracing the point of view of histology, physiologic physics and chemistry, pharmacology, and bacteriology make it possible to find a clue to causation in the connection between the disease and the medication used. As Pusey wrote, "Certainly no foreigner except Hebra compares with Unna in his influence upon American dermatology."

J. M. H. MacLeod, a student of Kaposi, Ehrmann, Caesar Boeck and Unna, in 1902 completed his 400 page Handbook of Pathology of the Skin, better described by its subtitle "An Introduction to the Anatomy, Pathology and Bacteriology of the Skin, with Special Reference to Technique," the first book detailing cutaneous pathological technique and normal and pathologic dermal histology in the English or any other language. This original edition and Unna's book on Histopathology of Diseases of the Skin, though both now antiquated, served their useful purpose admirably, and have been followed by a number of noteworthy textbooks on the subject, among the more recent ones the second editions of those of Gans and Lever.

In North America, Sigmund Pollitzer, after graduating from Columbia University's College of Physicians and Surgeons, in 1884, went abroad and worked with Virchow, Unna, and Malcolm Morris. He translated Darier's textbook into English in 1920. Pollitzer was, for his time, an expert histopathologist. Andrew Rose Robinson, of Ontario, Canada, studied in London, Paris, and Vienna after receiving his M. D. from Bellevue Hospital Medical College, in 1868. He was a pioneer histopathologist, a bent developed in his work abroad. On his return, Robinson taught histology in New York and was the first to describe hydrocystoma. Among other early United States microscopists were Sarah Elizabeth Finch, John Addison Fordyce, John Frank Fraser, William Samuel Gottheil, Meyer L. Heidingsfeld, Louis Heitzman, Thomas Casper Gilchrist, John T. Bowen, Joseph Jones, Ernest Wende, and Samuel Sherwell.

There was also Walter James Highman, who studied chemistry at Strassburg and Pathology at Prague, did postgraduate work in Berlin, Freiberg, Paris, Vienna, and Berne, and who was one of Jadassohn's disciples. Around 1917 Highman apparently began to suffer from an overreaction against dermatohistopathology, probably because too much was claimed for it. Thus, his council of caution, his stressing of the limitations of dermatohistopathology, was undoubtedly valuable, although expressed in his somewhat caustic manner. Highman thought that histopathology was indispensable for a basic understanding of skin diseases but that it had little practical value. Dermatohistopathology is neither as narrow and finished as claimed in 1918 by Moses Scholtz and Walter Highman, nor as broad and total as generally claimed in 1880. It is a growing field. For example, in Maximow and Bloom's new textbook of histology, we find five photographs showing five stages in the microscopic resolution of the structure of striated muscle—from the long fibrils depicted by Leeuwenhoek in 1682 to the myofilaments and cross bridges seen in the very-high-power electron micrographs of today. These five photographs may appear totally dissimilar to the untrained eye, and yet none contradicts or negates any of the others. The "dead skeletons" of cells are correlated with the living cells, the structure with the function.

Then there was David Lawrence Satenstein, who studied pathology in Vienna and Berlin and who sought to make a superspecialty of dermatohistopathology in America. Unfortunately, he never completed his articles on histopathology, which were to be the basis for a textbook.

Frederick Deforest Weidman, says Pillsbury, is the first American scientist to have devoted himself solely to basic laboratory research and teaching oriented toward the problems of diseases of the skin. He embarked upon this career in 1917, following eight years of basic training in anatomy, histology, and general pathology. An important observation made by him dealt with pseudoepitheliomatous hyperplasia at the margin of cutaneous ulcers; it would be difficult to estimate the number of patients who have been spared unnecessary destructive surgical procedures on the basis of this observation.

A vast amount of credit is due those of our contemporary dermatologists who have clarified many dermatological problems through their interest in dermatohistopathology, and, fortunately, a new vigorous generation is already evident. In every section of this country there are now expert dermatohistopathologists available for microscopic interpretation of biopsy material.

The greatest single factor in the acquisition of knowledge of cutaneous histopathology by dermatologists in general in this country is the mandatory requirement by the American Board of Dermatology and Syphilology of at least a basic working knowledge of dermal histopathology as one of two prerequisites to becoming a Diplomate of that Board. Interest in and knowledge of dermatopathology in America have been markedly enhanced by the impetus resulting from the Clinico-Pathologic Conferences and the pathology courses offered by the American Academy of Dermatology and Syphilology.

Microscopically, we can usually settle the diagnosis of some of the chronic inflammatory dermatoses, such as psoriasis, lichen planus, and lupus erythematosus; of most of the granulomas, such as syphilis, leprosy, and tuberculosis, including most of those of fungus origin, such as blastomycosis, coccidioidal granuloma, and histoplasmosis; and of nearly all of the tumors, such as carcinoma, nevi, and leiomyoma. Microscopic examination is even helpful in the differentiation of pigmentary disorders, such as hemochromatosis, Addison's disease, and pigmentation from heavy metals, as well as in some of the hypertrophies, atrophies, dyskeratoses and metabolic diseases. It should be remembered that biopsy and culture are the two definitive methods for diagnosis of systemic fungal infections and that all of the pathogenic fungi can be microscopically recognized.

Let us not forget that dermatohistopathology often verifies the diagnosis of systemic diseases as well as "skin" diseases; many cases of leukemia and other lymphoblastomas are on record in which the initial diagnosis could only be made because of the cutaneous manifestations and their histologic study.

Among numerous examples of the effect of histopathology on treatment we may mention leukoplakia; in this condition, if the histologic changes are those of ordinary leukoplakia, the area may be destroyed by electrocoagulation. On the other hand, if there are frankly anaplastic changes, surgery or ionizing radiation is indicated, as holds true for proper management of many other disorders.

Of all laboratory methods for dermatologic diagnosis, there is none that has as wide application as the biopsy. It is essential in almost all patients with chronic dermatoses, in all pigmented nevi which are excised, and in any lesion in which there is the least suspicion of malignant change.

Skin biopsy is proving useful even in the determination of chromosomal sex. This simple method provides a sure means of distinguishing males from females and thus eliminates laparotomy in pseudohermaphroditism.

Other areas being explored in recent years and of possibly great future significance include the histologic study of the skin in different age groups in order to test the effects of aging and exposure and the possibilities of neurohistologic studies in dermatology or those of the histologic changes of the skin in relation to dietary fat and to other aspects of nutrition.

It would be superfluous here to list all of the skin diseases in which microscopic examination of biopsy material settles or aids in the diagnosis, these having been adequately covered in the literature and textbooks, but I hope that the few I have mentioned may serve to indicate the wide field of dermatology and even of internal medicine and endocrinology in which microscopic examination of biopsy material is of diagnostic value. It is imperative here, however, that we acknowledge the value of

this procedure as a paramount debt of dermatology to dermatohistopathology.

We all agree that at times clinical judgment supersedes histopathologic findings, as in the premycotic stage of mycosis fungoides; this is true despite the fact that it is often possible to recognize mycosis fungoides histologically even in the early eczematoid or so-called premycotic stage of the disease, at which time the clinical diagnosis may only be suspected. However, there are times when both clinical judgment and microscopic findings falter, as illustrated by the fact that it is not invariably possible to distinguish keratoacanthoma or cutaneous horn or marginal proliferation of chronic ulcers from squamous-cell carcinoma.

Here and now probably is as good a time as any to admit, as Oscar Gans has stated, that, in spite of the impressive merits of dermatohistopathology, we must not forget that the basis for all dermatological diagnosis is morphology and that the time-honored method of refined inspection of the Hebra and Vienna School must be considered the "sheet anchor" of dermatology. However, who can deny that histology is in reality microscopic morphology and that dermatohistopathology is our most important "tool?"

The increase in the number of skin biopsy specimens microscopically studied is in itself an acknowledgement of dermatology's debt to and respect for dermatohistopathology. But precisely what is this debt?

Knowledge of dermatohistopathology is not merely an intellectual asset—I should not say "merely," because one must not minimize intellectual assets or real gains of insight into and understanding of skin diseases—but it is also of practical importance, and is of value not only for investigative purposes but for the diagnosis, prognosis, and treatment of many skin diseases. In fact, the primary purpose of histologic examination of biopsy specimens is to provide useful clinical information that will aid in the care of the patient. Histology has brought the methods of the exact natural sciences to dermatology.

Perhaps the greatest service pathology has rendered to medicine is its tendency to direct interest from the hazy atmosphere of speculation down to the hard earth of facts that must be accounted for. This is well illustrated by the discussions of clinical cases presented at dermatological society meetings. A well-prepared section, from a biopsy specimen taken with good judgment, will put to rest many fancy speculations. Just as the clinicopathologic conference has made the internist reasonably modest about his diagnostic ability, similarly the dermatologist who checks his diagnostic acumen by frequent biopsies tends to temper his pride.

Have we paid our debt to dermatohistopathology? I fear not, because it will never end. In fact, since the advent of the electron microscope, only 15 years ago, no other period has held as many advances in the knowledge of minute structure as the last decade—and this includes the almost 300 years that the microscope has been in use for the study of biological materials.

While some of the old histologic problems have been solved, many new ones have arisen with the new analytic methods and new points of view, as well as with the new instrumentation. Let us mention histo- and cytophysiology, as well as histo- and cytopathology; it is here that correlations are sought between morphology and functional activity and between morphology and disease processes. The entire field of cytology, of course, is really that of histology, since histology is the study of tissues and tissues are composed of cells.

Whereas, a few decades hence one might conceivably extol researches in physiology, bio- and histochemistry, and genetics as being responsible for the latest great advances in our knowledge of dermatology (and an idea of the strides accomplished in cutaneous physiology and biochemistry

is evident in Rothman's recent monumental book on the Physiology and Biochemistry of the Skin, and in dermatohistopathology in Beerman's and Pillsbury's recent comprehensive publication in Laboratory Investigation on Dermatopathology as a Field of Research), today it must be apparent to all of us that dermal pathology in the last few decades has been largely responsible for the high plane attained by our specialty, just as general pathology has so greatly influenced the position of internal medicine. With the submicroscopic world now coming into view and, among other things, the fusion of some aspects of biochemistry and biophysics with histology, an exciting new chapter is being written.

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The Unusual in Psoriasis

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An accurate description of the lesions and the course of psoriasis vulgaris is given as a definition of the disease in most of the old and modern textbooks on dermatology, but psoriasis vulgaris, as the name implies, is the common variety. Unusual manifestations of the disease may occur simultaneously with the ordinary type, or rare forms may exist without the presence of the ordinary lesions which would aid in identifying the bizarre manifestations. When such rare forms appear alone, diagnosis is often difficult and opinions must be separated from facts.

Obviously the morphology and the histology of the lesions offer the only basis upon which to make a diagnosis. There is a tremendous variation in the morphology of the odd forms of psoriasis, and if one has a large experience with the histopathology of the disease one knows only too well that what to the casual histologist is a simple pathologic pattern to the more experienced and critical observer often is a very difficult and perplexing problem. In controversial cases the histology may be more conclusive than the morphology, and in such indeterminate cases long observation may be necessary, possibly even until a classic lesion appears on another part of the body.

Psoriasis vulgaris may be dispersed over a large part of the body surface, but, despite its wide distribution and its frequency of occurrence, its microscopic anatomy is so closely related to that of many other eruptions that the boundaries for inclusion under the term are hard to establish.

In an effort accurately to define psoriasis we must appreciate that diseases such as squamous eczema, lichen simplex chronicus, seborrheic dermatitis, and lichen planus, to mention only a few of the more prominent ones, when they vary from their accepted common form may be almost indistinguishable from psoriasis both macroscopically and microscopically.

In order to attempt an explanation of the rarer forms, one must be acquainted with the evolution of the ordinary form, for rare forms must come from an accentuation or excessive development of one or several characteristic features of the well-known kind. Also the anatomic peculiarities of the involved part decidedly may alter the appearance of the eruption.

The cause of psoriasis is unknown, and none of the proposed theories are even indicative of which tissues are first involved. Therefore, the aberrations from the average cannot be interpreted as being due to distinctly confined activity. Whether psoriasis begins with epidermal changes or with alterations in the cutis has provided a good topic for debate, but no conclusion has been reached. Personally I lean toward the theory of an internal, possibly hematogenic, causative agent, combined with pressure, trauma, or some other environmental factor which accounts for the commoner localizations. Keeping in mind the interplay of these internal and external factors, one may explain to some extent the unusual forms.

Psoriasis in Childhood

Psoriasis is rare before puberty, and when it does occur in the very young it

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usually is not of the classic type. Three unusual forms may be encountered in childhood.

1. *Psoriasis Follicularis or Psoriasis Follicularis Spinulosa.*—This variety may be manifested by patches of horny spikes occurring at anterior tibial and olecranon areas, or the eruption may be fairly widely distributed so that it is difficult to distinguish from pityriasis rubra pilaris.

In the localized variety the area is dry and has a sheen as if varnished, and the follicular lesions may become apparent only when the area is lightly scratched. If other lesions indicative of psoriasis, such as marked scaling of the scalp, are present, they are helpful in diagnosis. Localized lichenoid lesions may have been present for a very long time and overlooked before more apparent psoriasis developed. If such an onset for psoriasis can be elicited, it is important that this be done, for psoriasis may be the result of metamorphosis in a predisposed area that has been subjected to pressure, trauma, or even infection.

Histologic examination of the lichenoid form of psoriasis surprisingly reveals that the process is not confined to the follicles. Although there are hyperkeratotic plugs, the immediately adjacent tissue shows areas of hyperkeratosis, parakeratosis, etc., allowing identification. In the widely disseminated cases histologic differentiation from pityriasis rubra pilaris is often difficult, if not impossible, despite the clinical findings.

2. *Psoriasis Guttata Acuta.*—This is the commonest form of psoriasis in childhood. It requires no detailed description, for it is well known to all dermatologists. It is important because of the systemic symptoms of angina and fever and because the eruption is spontaneous and exanthematic. This form offers rather convincing evidence in favor of an internal causative agent, and, since the eruption frequently disappears in a rather short time, it offers evidence in favor of the possibility of an immunizing factor. When one realizes that many people have some evidence of psoriasis, such as pitted nails, follicular lesions in the anterior tibial region, or scaling plaques at the elbows, and still do not develop psoriasis and considers, in addition, the uncertainty of inheritance of psoriasis, one may well entertain the possibility of inherent or acquired immunity.

3. *Localized Cephalic Psoriasis.*—Children may have localized, diffuse, or follicular psoriatic lesions confined to the scalp which may remain confined there and offer much difficulty in the differential diagnosis from fungus infection and the like. Especially confusing is the variety in which the scale collects in a cylindrical manner about the hair shafts. Diagnosis of isolated scalp psoriasis depends upon awareness and a careful differential consideration. Histologic examination of scalp lesions may be very perplexing. To be sure, discovery of psoriasis elsewhere is of great help. Examination of the tibial and elbow regions may yield the determining clue.

Psoriasis in the Aged

Psoriasis may develop for the first time in persons of extremely advanced years. Although it usually is of the ordinary type, it may be widely spread and often involves the cheeks. The lesions may be misleading, because of the senile atrophy of the integument; they may be red, almost transparent, and there may not be any collection of scales, because of the varnish-like tough coating. The plaques on the cheeks resemble lupus erythematosus, while those on the legs are suggestive of acrodermatitis chronica atrophicans. Microscopically, there may be only patches of parakeratosis with little acanthosis or hyperkeratosis. Occasionally psoriasis in the aged progresses to universal or erythrodermic proportions. Diagnosis is not difficult if one takes into consideration the peculiarities of the senile skin.

Confined or Localized Psoriasis

Psoriasis may remain strictly confined to particular anatomic areas, and when this is the case diagnosis is difficult and often

dubious, because a single localization is uncommon. The axillary, cubital, popliteal, inguinal, anal-scrotal, genital, nuchal, plantar, and palmar surfaces are such areas. At times several of these areas may be involved simultaneously.

Localized psoriasis of the axillary, inguinal, genital (except the glans penis), and scrotal areas is nearly identical morphologically. The lesion is a solid plaque; it is not composed of an aggregate of smaller lesions. Usually no satellite lesions are noted. The plaque is sharply demarcated from the surrounding skin, is red in color, is decidedly thickened, and is hard and brittle, thus being conducive to painful fissure formations. Scales may not be apparent but may be demonstrated by stroking. The lesions are resistant to treatment and may remain in situ for a very long time. Microscopic examination reveals marked hyperkeratosis such as is seen in lesions of so-called psoriasis rupioides. In the natural folds of the skin, as in the gluteal cleft, such lesions appear white and sodden and may even be moist.

Lesions of the glans penis are well known to dermatologists. The entire glans and the internal lamella of the prepuce (if present) may be involved, but more commonly there are a number of small scaling papular lesions on the dorsum of the glans. However, more diffuse involvement of the frenulum is occasionally seen. Aside from seborrheic dermatitis and lichen planus, diagnosis in this area is usually not difficult, although inguinal adenitis may be present and may lead one astray in making a diagnosis. As a rule, there is no adenitis adjacent to areas of any other type of psoriasis. The more serious diseases, such as Bowen's disease and erythroplasia, are verified microscopically. In elderly patients who have a constricting phimosis, psoriasis of the glans penis may cause much discomfort because of maceration and an odorous purulent discharge.

Psoriasis confined to the nuchal area always offers a diagnostic problem. Neither morphologic nor microscopic study may be conclusive. Such plaques are dry, but because of itching they may show excoriations and thus be dotted with crusts. Differentiation from the other members of the so-called nuchal complex requires careful evaluation. Psoriasis confined to the nuchal area occurs almost exclusively in women past the menopausal years, although I have seen a few examples in teen-age girls.

The hands or the feet, or both, are often involved in psoriasis, the lesions occurring either in conjunction with the ordinary type or alone. Because the hands or the feet may be the seats of so-called pustular psoriasis, such areas require particular attention. If the feet and hands are merely taking part in a widespread process, there is no need for more exact description.

Keratodermic psoriasis is manifested by sharply defined or scaling plaques. There usually are several present. The thenar and hypothenar eminences are common locations, although any part of the hands may be involved. The plaques are covered with dry thin adherent scales which, because of the constant use of the hands, do not accumulate, and, also because of constant use, the plaques often appear slightly depressed and are of a dirty gray color. At the periphery there is slight undermining. Scratching does not produce pinpoint bleeding, because of the nature of the palmar (and plantar) tissue.

The plaques may saddle the external lateral border of the hand, and the dorsal lesion then may be characteristic. Often periungual lesions are also present, and they may cause subungual keratomas. If these are severe, the nail plate may be elevated and the distal half entirely detached from its bed. Rarely does psoriasis confine itself to the periungual areas. Periungual psoriasis may be seen, too, when there is arthritis of the fingers. At such times there may be marked damage to the distal phalanges, with almost complete destruction of an absorptive type.

Psoriasis of palms may be and often is in some manner related to the occupation of the patient. It is much commoner in manual

laborers, and the medicolegal aspect of palmar (and plantar) psoriasis must be kept in mind. I have a number of times been a consultant to industrial boards when palmar psoriasis was judged to be the cause of total inability of the patient to continue with his work.

The entire question of pustular psoriasis has often been debated, and divergent schools of thought have resulted. That pustular lesions occur on the hands and feet as part of ordinary psoriasis cannot be denied, but when such lesions are confined, diagnosis is most difficult.

It is needless to attempt to make a descriptive differentiation between pustular psoriasis and the other possibilities, for a diagnosis based on morphology seems to me impossible. True, minute differential points have been neatly listed whereby pustular psoriasis was sharply contrasted to acrodermatitis continua and pustular recalcitrant dermatitis, but actually there are no unequivocal identifying signs. Moreover, the eruptions are not monomorphous, and there are various combinations and mixtures, thus making hard and fast differentiations untenable.

If it is conceded that any one of the cardinal pathologic changes in psoriasis may become greatly accentuated, then it may be admitted that the usually minute Sabouraud-Monroe abscesses could develop into larger, grossly visible abscesses and dominate the process. However, if that were possible, one would expect to find such a condition at least occasionally in other locations as well as in the form of a localized finding in ordinary psoriasis, but all students of psoriasis know that this does not occur. Furthermore, if all the lesions of a patient are pustular, again the diagnosis of psoriasis is in doubt. For my own part, I am willing to use the term pustular psoriasis for lesions which are being called that but which morphologically, microscopically, and in their response to treatment are admittedly far from being psoriasis as we now know it.

Generalized pustular psoriasis is a very severe form of psoriasis. It may develop in a person who has ordinary psoriasis or it may begin as the ordinary type. It may consist of a mixture of dry scaling and pustular lesions. The condition has distinct morphologic, systemic, and microscopic characteristics.

A fully developed case consists of many lesions which, as a rule, are widely disseminated and tend to remain as individual lesions rather than to coalesce into plaques. The classic lesion is elevated and has a red halo, or base, and a dark crust which, when removed, reveals a pus cavity in the center of the lesion.

The patient often has a persistently elevated temperature, accompanied by angina and occasionally by mucosal lesions which resemble erythema multiforme. Almost all patients with generalized pustular psoriasis have some degree of arthritis, especially of the extremities. Periungual lesions frequently are associated with distal arthritis. Lesions of the glans penis in a male patient are often present, and nonspecific urethral discharges have been recorded.

Microscopically the lesions show a superficial central accumulation of leukocytes and remnants of parakeratotic scales, forming a crust, or dry abscess. Beneath this crust more or less characteristic changes of psoriasis vulgaris are found.

The entire picture closely resembles that of Reiter's disease according to our present-day concept and that of parakeratosis gonorrheica of the older reports. In fact, it strongly suggests that Reiter's disease may be a primary acute form of generalized pustular psoriasis in which the patient develops an immunity to ordinary psoriasis.

Generalized pustular psoriasis is a debilitating disease requiring hospitalization and prolonged care.

Articular inflammation in psoriasis is always a sign of severity; in fact, it is an indication of systemic participation. Thus, one may divide psoriatics into two groups, those whose lesions and symptoms are entirely cutaneous and those in whom there are undoubted signs of other associated bodily ailments. I believe that we all recog-

nize psoriatic arthritis. Patients with the identical form of arthritis without skin lesions are occasionally the cause of speculation on the part of rheumatologists. Just as in lupus erythematosus, where the disease exists without skin lesions, the possibility of a systemic form of psoriasis without skin lesions should be contemplated, and if a test such as the L. E. phenomenon should be discovered we might greatly enlarge our concept of a common skin disease which has been viewed and studied too long as a purely cutaneous derangement.

Heredity is an established fact in psoriasis. Maybe future studies will show that ancestral arthritis could be a link in the genetic chain.

I believe that renewed studies should be made of psoriatics, especially the severe cases, with the hope that etiologic factors may be found that might point to the cause of this troublesome disease.

There are many more unusual manifestations of psoriasis that I do not have time to deal with in the time allotted. I can heartily recommend to all dermatologists to study the voluminous early literature on this disease. It is amazing to discover that the most enlightening and comprehensive studies were done at the time of Hebra and by those who immediately followed him.

Medical Arts Building.

Biochemical and Physiological Clues to the Nature of Psoriasis

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It is a great privilege and honor to be here today to give one of the John E. Rauschkolb Memorial Lectures. Many of us knew Dr. Rauschkolb personally, and I am certain that all of us who did must realize that the greatness of the Academy is in large part the result of the constant devotion and energy he gave to the Academy. Societies must never be viewed as arising and developing spontaneously. They always derive origin, power, and scope from men, from leaders like John E. Rauschkolb.

When our late beloved president, Nelson Paul Anderson, asked us to discuss the physiology and chemistry of psoriasis, he did so with full knowledge that we had done no experimental work in this field. We accepted the invitation with just this proviso: that we be allowed to appear before you as reporters of the old as well as the recent in the study of the basic nature of this common yet baffling problem of psoriasis.

The paper we are to present is a literary tour. It will give the salient findings of a library trip which took us through hundreds of books and journals. It is an attempt to survey all of the known chemistry and physiology of psoriasis. Its purpose is a clinical one: a better understanding of what psoriasis is. We hope that it will provide a firmer basis for understanding the disease. We further hope that it will stimulate interest in this field as an area of profitable research for both the clinician and the basic scientist. Such hopes are silently shared by several million psoriatic patients in the United States. We say "silently" because by and large psoriasis is a hidden disease. It is a cutaneous disease, yet one covered by clothing; it is one which has never excited public sympathy or even reached general public awareness. Only recently there have been some encouraging efforts to change this by acquainting the public with the significance and extent of psoriasis and by directing some medical research support into this sector.

Our survey must of necessity be brief. It will be directional, rather than inclusive, and somewhat dogmatic, rather than diffuse. For the comprehensive, one can turn to whole books written on the subject of psoriasis.[1-5] Special attention should be directed to Margarot's review [6] and to Rothman's book,[7] which discuss psoriasis from many basic considerations. Several recent reviews have also appeared.[8-10] In addition, we consulted over 500 articles and yet left the library knowing that many facts regarding psoriasis were still lost to us, since many authors failed to use psoriasis in the title of their papers. We have generally held these nonindexed items to lack impact, since otherwise the author would have entitled his article, "Psoriasis." It was our finding that, despite the wealth of material written about the chemistry and physiology of psoriasis, singular significant undisputed facts are rare. Certainly not all of what we will recount will be indisputable, but we have tried to look for the singular and the significant. In this regard the paper is divided into three major sections: characterizations of (1) the patient, (2) the eliciting stimulus, and (3) the lesion itself. From each section certain broad unifying concepts may be derived.

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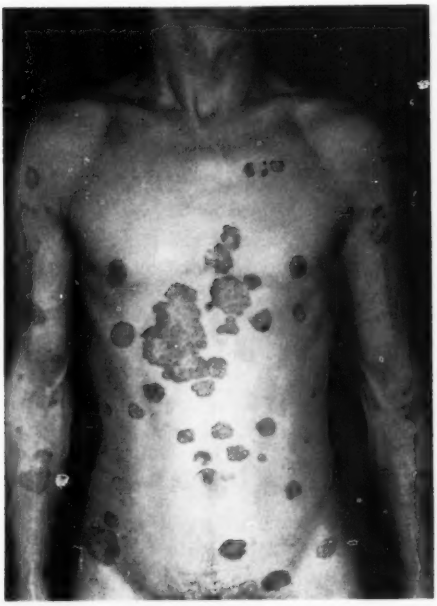

Fig. 1.—The psoriatic patient is to be characterized only by his hereditary background.

I. Characterization of the Psoriatic Patient

Is the riddle of psoriasis to be solved by a study of the patient? Can we actually characterize the person (Fig. 1) who has had, has, or will have psoriasis?

A. Chemistry.—Many, many studies have been made in this area. Psoriasis is common, and its obscure nature has invited all forms of laboratory study of the patient.

Table 1 outlines the blood studies which have been reported. In no way are any of these values uniformly or significantly altered. Debate, however, still rages in certain sectors. These include the various serum protein fractions. Some view the γ-globulin and lipoprotein fractions as often elevated. Others fail to confirm these observations. Again, the blood volume and the uric acid level are viewed as being elevated in certain psoriatic patients. These findings require further study before they can be accepted. In essence, however, there appears to be no way to identify the psoriatic by his blood chemistry.

TABLE 1.—*Blood Studies Showing Essentially Normal Values in Psoriatic Patients* *

Study	Reference No.
Hematology (count, coagulation, volume groups)	6, 11-13
Proteins	
Electrophoretic pattern	14-25
Peptidases	26
Carbohydrates	
Glucose tolerance	27, 28
Glucosamine	29, 30
Amylose	31
Lipids	
Cholesterol tolerance	32, 35
Cholesterol esterase	36
Fats	24, 35
Lipase	37
Minerals	
Na, K, Mg, Ca, P	38, 39
Miscellaneous	
Alkaline phosphatase	40
Uric acid	41, 42
Cholinesterase	43

* Some references are to the contrary.

Much less work has been done on the chemistry of the uninvolved skin of the psoriatic. Unconfirmed reports suggest that the sugar content is somewhat above normal.[28] The pitfalls of sugar determination in skin suggest caution in accepting these data. Studies on the skin peptidases show these to be entirely normal.[26,44] Sweat urea levels are normal.[45] Conflicting reports exist on the cholesterol metabolism of the skin.[46-48] Finally, the psoriatic is felt by one observer to excrete less than the normal quantity of biotin[49] in the urine. Urinary studies have been otherwise noncontributory.[6]

B. Physiology.—A recent extensive investigation[50] of the over-all nitrogen and sulfur metabolism of two male psoriatic patients has failed to reveal any abnormality, thus negating Schamberg's old time-honored finding that nitrogen retention was characteristic of psoriasis.[51]

The uninvolved skin itself has been a subject of scouting by many observers. L. Gougerot[52] found the impedance of such skin to be abnormally high. This phenomenon of heightened electrical resistance to alternating current (4000 cycles per second) is an entirely new finding, suggesting a constitutionally different type of skin in the psoriatic. An interesting conjuncture is

Madden's unconfirmed contention[53] that the uninvolved skin may show histological changes suggestive of psoriasis.

Milberg has studied the reactive hyperemia response in patients with psoriasis.[54] He finds evidence of an abnormality in the uninvolved skin in that reactive hyperemia is considerably delayed in appearance. Graham[55] has found that psoriatic patients show characteristic cutaneous vascular changes during stressful interviews. These consist of slight increases in skin temperature (arteriolar dilatation) and significant increases in reactive hyperemia time (increased tone of the minute superficial vessels of the skin). Plethysmographic studies by Huff and Taylor[56] also give evidence that the vascular system is involved. They found abnormal peripheral pulse wave tracings in the psoriatic.

Midana and Dogliotti[57] have interesting histologic evidence that the reticuloendothelial system is more active in the psoriatic. Various lipids (cholesterol, stearic acid, cerebroside, hydrous wool fat [lanolin], and olive oil) introduced into the skin were more rapidly removed from the skin of the psoriatic than from the skin of normal controls.

Depaoli has demonstrated that psoriatics show a normal rate of sensitization to 2,4-dinitro-chlorobenzene.[58] However, in the chronic psoriatic plaque this process proceeds at a slower rate than in normal skin. Strangely, the psoriatic patient does show an unusual sensitivity in that he may develop a true exfoliative dermatitis as a result of the systemic use of quinacrine (Atabrine).[59-61] This develops in two to four weeks and is of an unexplained nature.

Many organs other than the skin have been studied in the psoriatic, but the results have been largely negative. Liver-function studies are usually normal,[62] although recent use of the hepatic punch biopsy reveals an occasional psoriatic with fatty- or toxic-type degeneration of the liver.[63,64] Duodenal function has been checked as essentially normal.[31,65] Likewise, the function of the pancreas has been assessed normal by the fact that the fat and nitrogen content of the feces are normal.[31]

Many studies on adrenal function fail to reveal significant evidence of any disorder.[66-70] The Thorn test as well as the 17-ketosteroid levels in the urine are normal. Finally, the electroencephalogram has been found to show abnormal tracings in many psoriatics.[71,72] The significance of this remains to be seen.

C. Heredity.—Chemistry and physiology fail to give us a proven parameter for psoriasis. There is no chemical or physiological determinant, and yet from the biological aspect there is one to be found in heredity. Much has been written,[41,73,74] but the observations and writings of Hoede[75,76] are the master contributions. Hoede has made an exhaustive search into all of the features of the heredity of psoriasis and forcefully concludes, "Es gibt keine Psoriasis ohne Heredität" (There is no psoriasis without heredity).

Racial differences in the incidence of psoriasis are impressive.[77,78] Lomholt, in a very careful study of 11,000 persons on the Faroe Islands, found an incidence of psoriasis of 2.84%. In contrast, psoriasis is rare in dark-skinned persons, such as Negroes or Indonesians.

The familial history of psoriasis may be striking. Lomholt found one family in which 34 cases of psoriasis were known to have appeared in just 5 generations. Psoriasis is an irregular dominant trait with imperfect penetrance, to use the geneticists' phrase. Yet all such heredity studies are limited by many difficulties. One must recognize that psoriasis may appear for the first time late in life or that it may have such an insignificant form as to fail to be noted in any medical history. Should a method be developed to detect the "psoriatic" in the absence of skin lesions, one might learn that the diathesis or the disease was transmitted in a completely regular dominant fashion. Actually in practice

only about one in three patients with psoriasis can give a history of other members of the family having had psoriasis.

Probably the clearest evidence of the hereditable nature of psoriasis is provided by the study of identical twins.[79,80] Haro's findings are especially pertinent. In a study of 21 monozygous twins, there were 13 instances in which both twins had psoriasis. In contrast to those findings for identical genetic material, in 13 dizygous twins there was only 1 instance in which both twins had psoriasis. These data are in strong support of a genetic pattern for psoriasis.

In summary, one can characterize the psoriatic patient as one who has a specific familial hereditary background. One cannot describe the mode of inheritance, and yet the fact of inheritance remains the single unchallenged fact about the psoriatic.

II. Characterization of the Eliciting Stimulus

One of the distinctive, yet tantalizing, facets of the riddle of psoriasis is the observation that at times the localization of disease can be experimentally controlled. The scholars of dermatology knew this over 100 years ago,[81] and yet it was Köbner, in 1872, who first wrote so convincingly of the phenomenon of local production of psoriatic lesions that his name has been inseparably linked with this observation.[82] This Köbner phenomenon surely offers clues as to the nature of psoriasis. Let us examine it carefully (Fig. 2). The papers of Lipschutz, Levi, Fleck, and Szodoray are the most valuable in this regard.[83-85] In its simplest form the Köbner reaction appears as a delayed scaling inflammatory psoriasiform lesion at the exact site of trauma. The latent period between local injury and the evolution of the lesion is usually 10 to 14 days, but it may be as long as 2 years.[86,87] The trauma must be through the epidermis and actually into the dermis. Simply scratching the corneum or the epidermis never leads to a Köbner response. Furthermore, minor vascular trauma, e. g., petechial formation,[88,89] is not followed by a Köbner reaction. A most significant finding in these studies is the fact that the Köbner reaction occurs only in patients presenting eruptive, florid, progressive, or active psoriasis. It would appear from this that the injury or trauma simply permits or directs the localization of the disease process. This has suggested to many that a circulating noxa or virus is released in the skin, but to others the concept of a local metabolic disturbance is a compelling one. It should

Fig. 2.—The Köbner response (following sunlight exposure, in this instance) occurs only as a result of nonspecific trauma during a period of exacerbation. It represents not experimental production of the disease but rather experimental localization.

be pointed out in this regard that pellagrinous patients show a form of the Köbner isomorphic reaction in that in this vitamin-deficiency syndrome lesions appear precisely at areas of local trauma (stasis, scars, burns, pressure, irritation, friction, and inflammation). Bean et al.[90] have felt that this localization resulted from local anoxia or from local increase in metabolic activity.

Nerve paralysis[91] and sympathectomy[92] have not been found to interfere with the localization of psoriasis. However, the Köbner response does tend to respect areas of healed psoriasis.[93] It does not occur in the involuting central portion of a psoriatic plaque. Nardelli[94] finds that epinephrine as well as inflammatory processes tend to locally inhibit the production of the Köbner response. The significance of these observations is not at all clear.

Much effort has been expended to determine the very first change occurring in the skin during the experimental development of a Köbner response. It has been assumed that such morphologic findings would point to whether or not psoriasis is a disease of the corium or epidermis. Such an approach is not altogether profitable, since, as soon as Szodoray[85,95] demonstrated that the capillary changes in the dermis precede all other morphologic change, Kuta and Neumann[96] showed that dehydrogenase enzyme changes in the epidermis precede the capillary alteration. Possibly the next rebuttal will be a demonstration of alkaline phosphatase changes in the capillaries following trauma. In any event, the primary site of the disease remains unknown.

Only one observer[97] views the Köbner phenomenon with distrust, stating that histologically the lesions produced are not true psoriasis but rather an abortive form.

Finally, the following lists indicate the elicitors of the Köbner response. These localizing stimuli for psoriasis are effective only during exacerbation. Experimental stimuli are as follows[81,83-85,88,97]:

Scarification
Electrodesiccation
Tape strippi g
Primary irritant

Clinical stimuli are as follows[84,92,99-113]:

Bites (insect, animal)
Burn
Dermatitis
Drug reaction
Excoriation
Incision
Lichen planus
Lymphangitis
Miliaria
Photosensitivity
Pityriasis rosea
Pressure (belt, truss, arch support)
Radiation (ultraviolet light, grenz ray, x-ray)
Skin tests (scratch, injection, tuberculin)
Vaccination
Vitiligo
Zoster

These are not the cause of psoriasis but strictly the agents or events which may determine localization whenever psoriasis is extending. It can be concluded that the localization of psoriasis is truly that of a reaction pattern.

III. Characterization of the Psoriatic Lesion

Is not the riddle of psoriasis truly within the very lesion itself? We have seen that the psoriatic has a hereditary background. We have seen that the localization of lesions is actually at sites of trauma. Now let us look at the lesion itself (Fig. 3). It is specifically a cutaneous change, since no systemic lesions are known to occur. It is a silvery-white scaling process. Indeed the scales dominate the entire clinical picture. Only after removing the scales do we fully realize the underlying erythema.

Turning to histologic study we greatly enlarge our knowledge of the psoriatic lesion.[114] Three key features are evident in Figure 4: the enormous active growth of the epidermis, the striking increase in the stratum corneum, and the remarkable proliferation of the subepidermal capillaries. A great number of chemical studies as well as physiological observations all

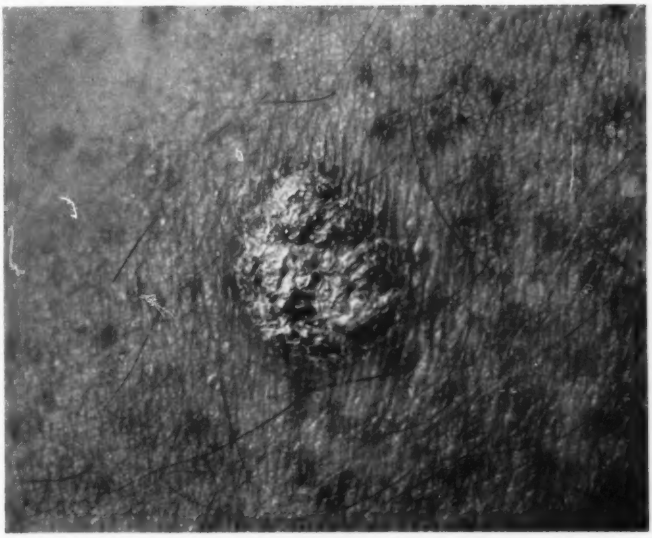

Fig. 3.—The lesion of psoriasis is a scaling erythematous patch. These are the scales which fail to bind water and which have a low amino-nitrogen content.

support and expand these histological findings.

The epidermis is actively growing. Very early studies of the cellular metabolism of the psoriatic lesion [115,116] revealed the oxidative processes to be taking place at a considerably higher rate than normal. More recently Stüttgen showed with the Warburg technique that not only was the oxygen utilization of psoriatic skin much higher than that of normal skin but also that anaerobic, as well as aerobic, glycolysis was considerably increased.[117] Steigleder and Szodoray and Sóvári, as well as Braun-Falco and Rathjens,[118-120] have confirmed this increase in oxidative capaciy by means of various histochemical means. Using the Nadi reaction to demonstrate oxidases and various tetrazolium salts to demonstrate reduction systems, they all find an increased

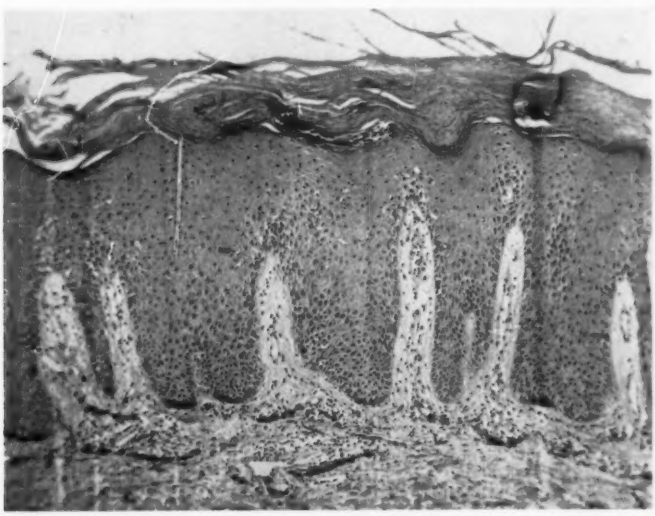

Fig. 4.—Histological view of the psoriatic lesion, showing acanthotic epidermis, parakeratotic scale, and dilated enlarged capillaries in the dermis. Hematoxylin and eosin; reduced about 16% from mag. × 80.

cellular activity in psoriatic lesions. Others have obtained evidence of the increased reductive capacity of psoriatic skin by injecting methylene blue or 2,6-dichlorphenolindophenol into the skin.[121-123] The dyes decolorize more rapidly in the affected areas. In all such studies the possibility of technical artifacts must be kept in mind. One point at which they might arise is recalled by Gans' old observation [124] that the psoriatic epidermis has an acid pH, between 5.9 and 6.6

Not only is the oxidation-reduction system in psoriatic skin increased, but other enzymes show an increased activity. These include both specific and nonspecific esterases, as well as alkaline phosphatase, β-glucuronidase, and arginase.[125-128] Finally, sundry other investigations support the view that the epidermis in the psoriatic lesion is operating at a heightened pace. One of these is Rothman and Felsher's finding that the insensible perspiration in psoriatic plaques is three to eight times that of normal skin.[129] In interpreting all of this work it must be recognized that the increased metabolism is not a specific finding. It is seen in association with many other epidermal changes.

The increase in stratum corneum or scaling is the second striking histologic finding in the psoriatic lesion. Looking closely we can see that cornification is abnormal, in that the cells retain their nuclei. This parakeratosis must make itself felt in all of the chemical studies which have been done on the scale. The chemistry of the scale has been a most attractive subject for biochemists, but here controls have too often been neglected. Too often we must say that there is no evidence that the observations or conclusions relate specifically to psoriasis. For example, the nickel content of the psoriatic lesion has been reported as abnormally high,[130] but lack of control data on other scaling lesions prevents assessment of this finding.

In any event, cholesterol has been found to be normal,[131] whereas the choline content of psoriatic scale may be high.[132] Zorn has reported the psoriatic scale to contain five to nine times more urea than there is in blood.[133] More pertinent observations by Zorn and later by Dihlmann [134,135] have revealed histamine in the psoriatic scale as well as a number of other amines: vinylamine, alkylamine, methylethylamine, dimethylethylamine, and trimethylethylamine. Tyramine and acetylcholine were not found in the dialysate of scales.

The protein chemistry of the scale has been an especial focus, since water-insoluble protein, keratin, is the major product of the epidermis. Many have viewed psoriasis as basically a defect in keratinization.[136,137] Early observers found that the sulfhydryl content of psoriatic scale is very high.[138] This has been repeatedly confirmed and adduced as evidence of an altered keratinization.[139-141] In 1955, Grüneberg and Szakall [142] reported an extensive series of chemical determinations on psoriatic scales. They found significantly that the scales contained much less water-extractable substance than do normal horny layers. The amino-acid pattern, however, was qualitatively the same as normal. This latter finding was confirmed by Hähnel,[143] who indicated furthermore that the scales had a low free-amino-nitrogen content.

Flesch and Jackson Esoda [144,145] have also actively engaged in a study of the psoriatic scale. They have disclosed a characteristic deficient water-binding property of this material. This has been associated with a high sulfhydryl content and a low free-amino-nitrogen level. Recently they have described a simple rapid laboratory test for the demonstration of the low free-amino-nitrogen content of psoriatic scales.[146] The test consists of a ninhydrin reaction in a fatty alcohol sulfate (Duponol) extract of a single scale. If the test is positive, psoriasis is eliminated as a diagnostic consideration. A negative test is compatible with the diagnosis of psoriasis and with certain other scaling dermatoses.

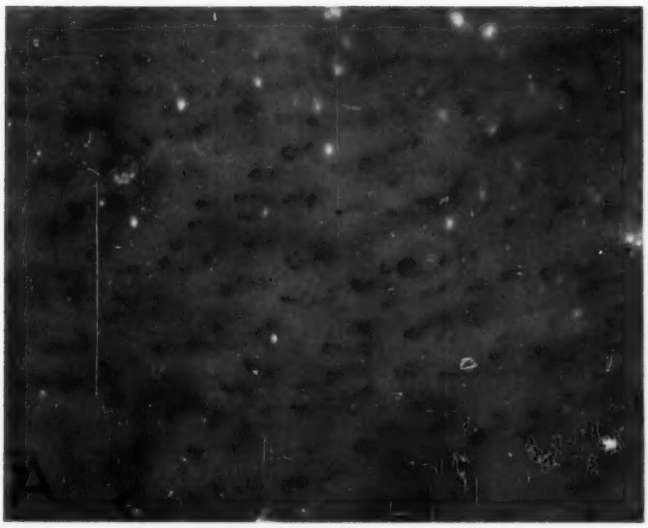

Fig. 5A. — Capillary vessels in normal skin as seen from surface view; reduced about 8% from mag. × 60.

The most recent work of Grüneberg and Szakall discloses an entirely new facet of the metabolic problem of psoriasis.[147] They have now demonstrated that the pentose levels in psoriatic scale are 3 to 10 times normal. Flesch and Jackson Esoda [148] have also found the pentose levels, both free and combined, to be regularly elevated in the psoriatic scales. It would appear that this chemical change is to be correlated with the presence of retained nuclear material in the scale.

The vessel growth in the psoriatic lesion is phenomenal (Figs. 5 and 6). This has excited notice since the time of Unna,[149,150] and recently renewed interest in capillary microscopy in vivo has pointed up the fact that the psoriatic capillary loop within the dermal papilla is dilated and curled up into balls or coils.[151] Many years ago Wor-

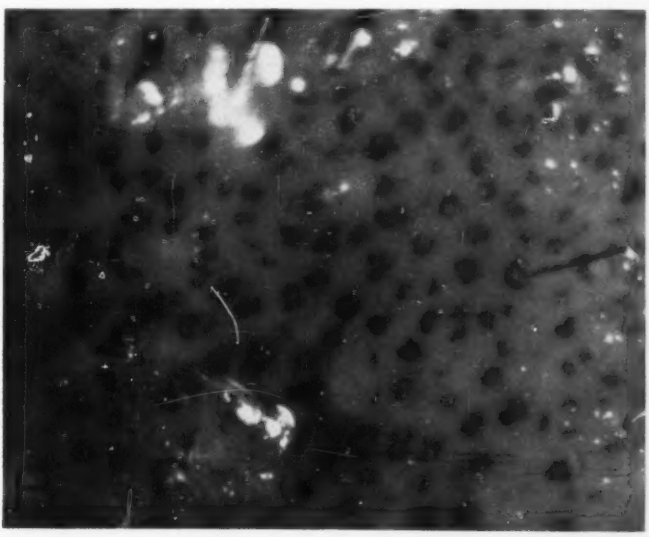

Fig. 5B. — Enlarged tufted capillary supply in psoriatic lesion as seen from surface after removal of the scale with cellophane (Scotch) tape; reduced about 8% from mag. × 60.

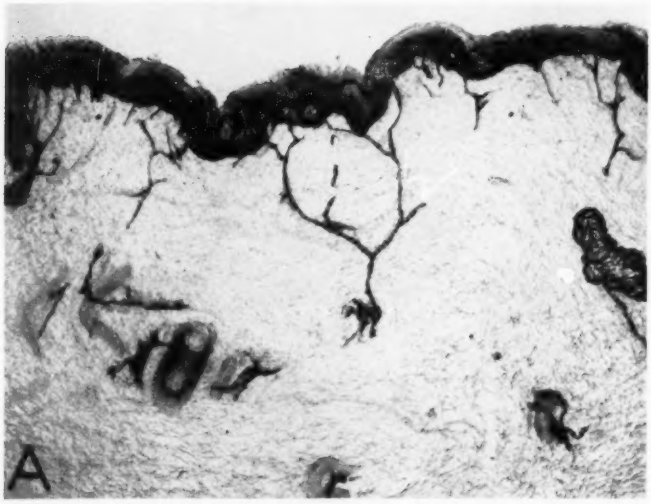

Fig. 6A.—Normal terminal blood supply in skin as revealed by alkaline phosphatase in thick section; reduced about 16% from mag. × 48.

ouoff [152] described a halo of vascular change about each psoriatic papule. This ring of Woronoff has been studied in vivo by Herrmann and Kanof.[153] After intravenous introduction of fluorescein they noted that each lesion was surrounded by a hyperfluorescent, sharply defined halo, which suggested increased capillary permeability as well as local stasis. Braun-Falco [154] has discovered that the endothelial cells of vessels in a psoriatic lesion display an increased phosphorylase content. This may be associated with the growth changes. Szodoray and his group [155,156] have recently been very active in the study of the nature of this vascular change, since they view it as the primary change in psoriasis. They find 10 to 100 times more acetylcholine present in the skin dialysate of psoriasis than in control dermatoses or in normal skin. Furthermore, they find that commonly cholinesterase shows an elevated level in both the lesion and the serum. They thus view the vasodilation of

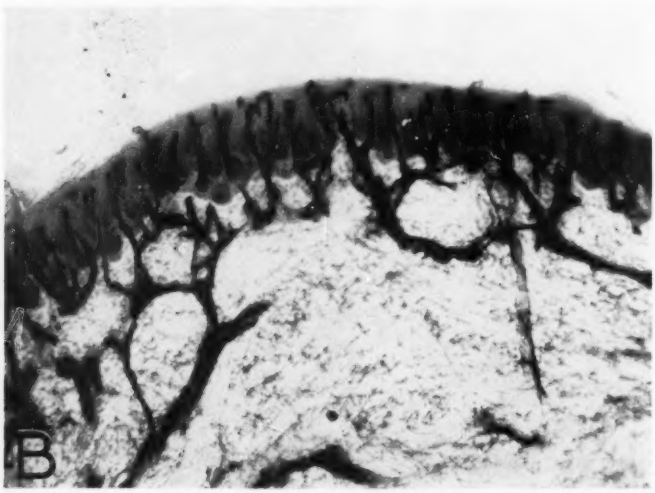

Fig. 6B.—Enormously enlarged and expanded capillary blood supply to psoriatic lesion; reduced about 16% from mag. × 48.

TABLE 2.—*Summary of Salient Chemical Abnormalities of the Psoriatic Lesion*

Abnormality	Direction
A. Lesion	
Water-soluble polypeptides	Low
Dipeptidase activity	Low
Zinc	Low
Oxidative enzyme activity	High
B. Scale	
Sulfhydryl	High
Pentoses	High
Nickel	High
Free amino nitrogen	Low
Water-binding property	Low
Dipeptidase inhibitor	(Present)

psoriasis as cholinergic in origin. All of the vessels contract in the presence of epinephrine, but only one-third will show any dilatation after the injection of histamine or acetylcholine. One can conclude from their papers that the vessels of the psoriatic lesion are under rather continual humoral vasodilator influences.

Garbi was one of the first to record the fact that psoriatic plaques are anhidrotic, both to heat and to cholinergic stimuli.[157] Others have confirmed this,[158,159] but Suskind has provided us with the most comprehensive study of the function of the eccrine sweat gland in the psoriatic lesion.[160] He finds that healed areas may remain anhidrotic for months after clinical healing. The glands appear normal and contain the normal amount of glycogen. His data may be interpreted to indicate that the anhidrosis results from sweat retention following poral occlusion. However, an alternate explanation may be advanced. Szodoray and co-workers[161] have found the cutaneous nerves in psoriatic lesions to show anatomic degenerative changes. Possibly the local anhidrosis reflects a failure of innervation. Further study should distinguish the precise nature of the anhidrosis.

Braun-Falco and Rathjens[162] have recently considered the possibility that psoriasis results from a zinc deficiency, since swine may develop a patchy parakeratotic scaling eruption purportedly as a result of a dietary deficiency in zinc. They did find histochemically that 11 of 14 cases of psoriasis had a lowering of zinc content of the lesion. However, no conclusions were drawn, as further study is under way.

No data could be discovered by us concerning the status of the lymphatics, the sebaceous gland, or the apocrine gland in psoriasis.

In the field of lipid metabolism, Grütz[163] vigorously championed the view that psoriasis was a lipoidosis, citing the lipophages to be seen in the psoriatic lesion. This concept has been completely overthrown, and Dogliotti has a very convincing review of the literature which concludes that although the lipid level of the psoriatic lesion may be increased this is a completely nonspecific finding.[164] Auken's monograph[35] also treats this subject exhaustively.

The carbohydrate metabolism of the psoriatic lesion has been studied repeatedly, with divergent results. Ribuffo[28] has just published an extensive review of all of the literature, and more data may be expected to appear. Much effort has been expended in observations of the epidermal glycogen.[165-167] No predictions can be made, since often the acanthotic epidermis is devoid of glycogen; at other times glycogen appears in abundance. Control studies of the glycogen level in correlation with the Köbner response may be rewarding.

It is in the field of protein metabolism that the signal advance has come. Paschoud and Schmidli made the breakthrough in 1955 by characterizing a specific psoriatic defect. In a brilliant paper these Swiss authors[168] found that *the psoriatic lesion regularly had a marked reduction in the amount of water-soluble polypeptides.* Twenty normal control values averaged 1363 mg. % (amino nitrogen) water-soluble polypeptides. The normal uninvolved skin of psoriatics in 11 determinations showed an average of 1299±95 mg. %. In contrast, the psoriatic lesion in 11 determinations averaged 556±50 mg. %. This finding was duplicated with or without scales. Control values for eczema were near normal. Finally the amino-acid levels

in the lesion were found to be entirely normal.

The following year Paschoud, Keller, and Schmidli[44] presented a masterful experimental analysis of the nature of this psoriatic defect. Their work, which appears to us to be dermatologic research in its finest flowering, convincingly demonstrated that *the psoriatic lesion is deficient in dipeptidase activity*. Specifically, leucylglycine and glycylglycine dipeptidase activity was studied. These dipeptidases are the proteolytic enzymes which hydrolyze proteins into the smaller water-soluble polypeptides. It is thus clear that the low polypeptide content of the lesion relates back to this enzyme deficiency. It is specifically the dipeptidases which fail in psoriasis. This specificity is shown by the fact that the tripeptidase activity is normal. Furthermore, Paschoud, Keller, and Schmidli showed this defect to be found only in the psoriatic lesion, not in the adjacent uninvolved skin. Numerous studies on other types of chronic inflammatory skin lesions showed that this enzyme failure was found only in psoriasis. However, other scaling lesions, such as seborrheic dermatitis, were not included. Later, Braun-Falco showed histochemically that leucine amino-peptidase levels were reduced in psoriasis.[169]

These ingenious investigators quickened their pace and showed that actually the dipeptidases are not chemically absent from the psoriatic lesion. By the addition of nearly 0.002 M cobalt to the psoriatic skin, dipeptidase activity soared to enormously high levels. They then knew that the enzyme was present. But why was it not active in untreated psoriatic skin? The scale provided the answer. By simply removing the scale from the psoriatic lesion they found that dipeptidase activity in vitro was restored to normal. It became evident that the scale contained an inhibitory factor. This factor could also be removed experimentally from the entire psoriatic lesion by differential precipitation and centrifugation. It is assumed by these investigators that this enzyme inhibitor is actually found throughout the lesion, but in vitro demonstration has been possible to date only with use of the scales, wherein the agent could be expected to be highly concentrated owing to the great quantity of dead cells there. The nature of this psoriatic enzyme inhibitor is still completely unknown. Possibly it is a metallic element. We await future reports with great interest.

Many questions have been answered. Many more appear! What are the nature and origin of this dipeptidase inhibitor? Can we expect to correct the dipeptidase deficiency by catalysts such as cobalt? What is the total picture of the protein enzyme chemistry in psoriasis? These and other questions become evident and significant as basic science provides new tools, insight, and knowledge of that common chronic disease psoriasis.

Summary

In summary, a review of the basic studies of the physiology and chemistry of psoriasis indicates that this is a hereditable disease, showing a distinctive localization pattern, and one in which the specific defect now appears to be in the enzyme systems concerned with the protein metabolism of the epidermis.

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The Recurrence of Nevi After Incomplete Removal

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Along with recent advances in the knowledge of pigment formation and of pigment-cell biology, there has been an increasing interest in the pigmented mole or nevus. Since it is an extremely common lesion, clinically often disfiguring, many patients are seen who desire cosmetic removal of their moles. A great deal has been written about benign pigmented nevi, their pathology, their relation to melanoma, and their treatment,[1] but little has been published about treatment failures and recurrence. It is the purpose of this paper to discuss various mechanisms by which benign nevi may recur after treatment and to evaluate the significance of such recurrence.

Several methods of dealing with the common mole are described in the literature. These may be divided into two main types: deep excision, which removes the entire lesion, and other methods, which do not completely remove it. Many dermatologists [2] feel that malignancy in the common mole can be reliably ruled out with expert clinical examination and that such clinically benign lesions may be safely removed by use of electrocautery, electrodesiccation, or by just slicing off the protruding portion.

After superficial removal of this type, which is used purely for cosmetic purposes, there must necessarily be a certain percentage of recurrence. In one series,[3] out of 129 small pigmented lesions, 4 were excised because of failure of previous treatment. In another series of 204 nevi,[4] 2 had had prior unsuccessful removal.

Two types of clinical appearance of these recurrences have been described. The lesion may reappear as (1) an area of pigmentation or (2) an elevation at the site of previous removal. Walton et al.[5] state that pigmentation remained in about half of their series of 168 clinical moles which were removed by slicing and light electrodesiccation but that in only 1 case of their completed series of more than 100 lesions which were followed and rebiopsied was there a definite recurrence of the lesion as a flat area of pigmentation.[6] Shaffer [4] described 2 lesions in his series of 204 nevi which recurred as doughnut-shaped elevations around the scar of the prior electrodesiccation. Traub [7] states that regrowth rarely takes place but does mention that pigment recurred at the site of an excised nevus.[8] Goldman et al.[9] mention recurrence of two junction nevi in the scars after removal. Becker [10] mentions a brown color or an elevation at the site of previous removal. Davis [11] states that incomplete electrodesiccation may be followed by rapid regrowth.

When our study was begun, there had been no systematic investigation of the mechanism and of the significance of these benign recurrences. Gougerot,[12] who observed nevi to recur in the scar of previously destroyed nevi, felt that this recurrence was due to seeding of the nevus cells during removal. This concept of the mechanism of recurrence continues to be upheld in Europe, where some feel that even biopsy of a pigmented lesion should not be attempted until

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From the Departments of Dermatology of Wayne State University and Receiving Hospital of the City of Detroit (Dr. Hermann Pinkus, Acting Chairman). Fellow in Dermatology, Wayne State University College of Medicine (Dr. Schoenfeld).

high doses of irradiation have been applied,[13,14] to prevent growth of any possibly seeded cells.

Recently, Walton, Sage, and Farber have done an excellent study of this problem.[5] They sliced off the superficial portion of the mole and cauterized the remaining denuded surface. The slice was examined microscopically to determine the exact nature of the lesion. After varying periods of time the treated site was rebiopsied and the specimen was compared with the earlier biopsy. They found that in no case was there any tendency toward malignant change in the lesion and that when there was a recurrence it resembled the original lesion.

Material

Our study concerns 19 cases of recurrent pigmentation after cosmetic removal of a mole. The site of recurrence was excised for microscopic study. The material presented is selected from biopsy specimens submitted to one of us by dermatologists in private practice. Complete data were not always available, but we feel certain that the original nevi were clinically benign and that they were treated purely for cosmetic reasons. The specimens were all fixed in 10% formalin or in 70% alcohol, cut in serial paraffin sections, and stained with hematoxylin and eosin, acid orcein-Giemsa,[15] and with a modified van Gieson stain.[16]

Interpretation of Findings

In our interpretation of the histologic findings we follow the generally accepted view [17] that most nevi originate at the dermoepidermal junction from the melanocytes which are present normally, through their multiplication and transformation into nevus cells. We agree with those who accept the neural crest origin of melanocytes and do not believe that they are modified epidermal basal cells.[18,19] We also agree that each nevus has a natural history,[20] beginning as a simple lentigo in which melanocytes accumulate at the dermoepidermal junction. These melanocytes form larger nests of nevus cells at this junction. Some or all of these nests may become detached from the epidermis and surrounded by mesodermal fibers of collagen, elastin, and reticulum. In the final mature stage of the nevus all the nests are in the dermis and none are left at the junction.

According to these three stages of development, nevi are divided into junction, compound, and intradermal lesions on histologic examination. It must be realized, however, that these terms refer only to the prevalent localization of the cell nests. Most junction nevi show some intradermal nests,

Findings in Nineteen Cases of Nevi Removed with Recurrence

Case No.	Age	Sex	Location	Duration, Yr.	Clinical Diagnosis	Method of Treatment	Time of Recurrence	Scar Tissue Present	Intradermal Nests Present	Junction Nests Present
1	15	M	Scapula	Many	Junction nevus satellite pig.	Excision	Few mo.	•	•	•
2	35	F	Shoulder	Many	Benign pig. nevus	Curettage, cauterization	2 mo.	•	•	•
3		F	Neck		Intraderm. nevus	Ablation	2 yr.	•	•	
4	22	F	Scapula		Elevated mole	Electrodesiccation	Few mo.	•	•	
5	27	F	Nose		Mole	Electrodesiccation	Shortly after	•	•	
6	41	M	Temple		Mole		6 wk.	•	•	
7	28	F	Cheek	Many	Pigmented mole	Electrodesiccation	With healing	•	•	
8	27	F	Nose		Pigmented nevus	Cauterization	4 mo.	•	•	
9	35	F	Upper lip		Mole	Cauterization		•	•	
10	35	F	Lower eyelid		Mole		Few yr.	•	•	
11	19	F	Back		Mole	Electrodesiccation	With healing	•	•	
12	45	F	Upper lip		Mole		15 yr.	•	•	
13	45	F	Eyebrow		Mole	Acid		•	•	
14	18	M	Nose	7	Mole	Electrodesiccation	1 yr.	•	•	
15	14	M	Shoulder			Electrodesiccation	1 yr.	•	•	
16	14	M	Forearm	14	Mole	Electrodesiccation	4–5 wk.	•	•	
17	18	M	Dorsum hand		Mole	Acid	18 mo.	•	•	
18	16	F	Finger		Verruca	Electrodesiccation	5 mo.	•		
19	19	M	Tip of coccyx	4		Electrodesiccation	4 yr.	•	•	

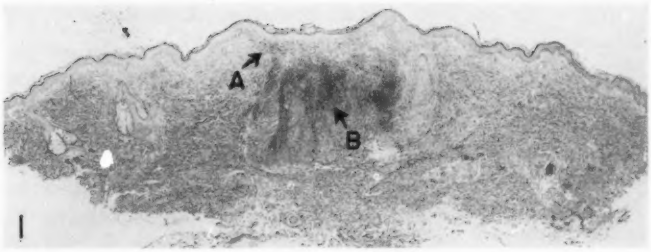

Fig. 1.—Recurrence of junction nevus (*A*) over incompletely removed pigmented intradermal nevus (*B*). Hematoxylin and eosin; reduced about 23% from mag. × 10.

and many mature, clinically quiescent nevi show some junctional nests. This latter finding increases in direct proportion to the number of sections examined from each individual nevus, and it is likely that fewer intradermal nevi would be recognized if each lesion were examined in complete serial sections.

The findings in our 19 cases are summarized in the Table. There are certain features common to these cases. The original lesion is diagnosed as a common benign mole and is incompletely removed. After a varying period of time, usually a number of months, pigmentation recurs. The tumor mass itself does not regrow.

The sections of the recurrent lesions show a rather uniform pattern. In all cases but the one in which the original lesion was probably a wart lying near a junction nevus, there are remnants of the original nevus present. These are seen as nests of cells lying in the pars reticularis of the dermis (Fig. 1). They show no signs of activity and are covered with a layer of fibrous scar tissue. This scar can be best demonstrated in the orcein-Giemsa-stained sections, in which the normal pattern of the elastic fibers is seen to be disrupted (Fig. 2). The scar, in turn, is covered with regenerated epidermis showing nests of nevus cells with varying amounts of pigmentation at the dermoepidermal junction. The first two cases are particularly instructive, since specimens of the original lesions as well as of the recurrent ones are available. The original lesion in each instance was a mature intradermal nevus with a few cell nests still present at the junction.

In some of the histologic sections in which there were remaining hair roots, we feel that the source of the recurrent junction nevus was nevus cells around the hair root. In other sections it is our opinion that the junction nevus cells have come from the periphery of the original lesion. This assumption is supported by those cases in which specimens of the original nevus are available for study. These show that the original lesion was an intradermal nevus with at least a halo of junctional nests at the periphery containing little or no pigment (Fig. 3).

From these facts it is deduced that the original lesion appeared clinically as a completely benign common mole without a halo of pigmentation evident on examination. This mole was removed by one of the commonly employed methods, by shaving the

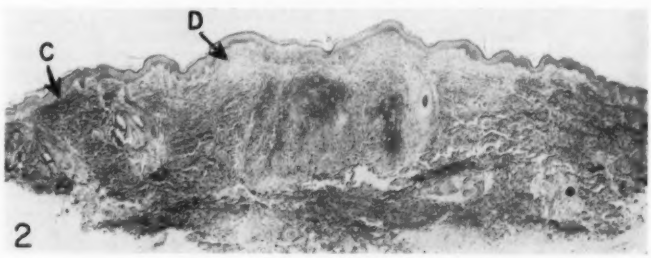

Fig. 2.—Same specimen as Figure 1, showing disruption (*D*) of the natural pattern (*C*) of elastic fibers, indicating previous damage. Orcein Giemsa; reduced about 23% from mag. × 10.

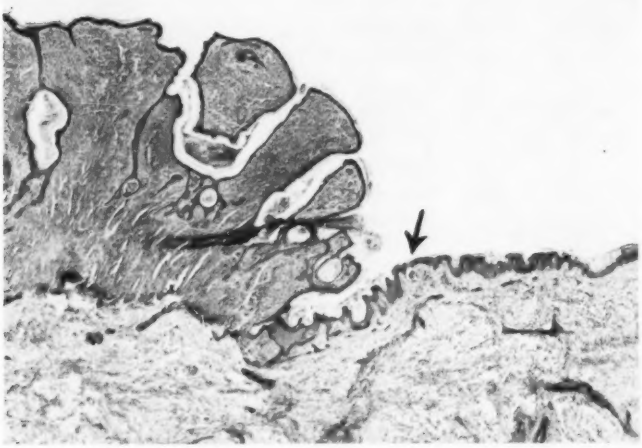

Fig. 3.—Junction nevus cell nests at the periphery of a quiescent intradermal nevus. Hematoxylin and eosin; reduced about 18% from mag. × 13.

top of the tumor off and then electrodesiccating the base or by electrodesiccating the entire lesion, in order to obtain an agreeable cosmetic result. Instead, pigment recurred, causing anxiety to both patient and physician. Apparently, when the epidermis grew over the defect it carried with it junction nevus cells which proliferated and produced the recurrent lesion and repigmentation of the area.

Comments

A number of years ago MacKenzie and Rous [21] observed in rabbit ears that a circular surgical defect which cut through an area containing pigmented cells healed with growth of the pigmented cells into the resulting scar concurrently with growth of the rest of the epithelium. Because the wound healed by concentric advance of the epithelium from all sides, the pigmented area became a linear streak, beginning at the edge of the circular defect and extending into the center of the resulting scar. It is seen that the regenerative abilities of pigmented cells roughly parallel those of the rest of the epidermis in the experimental animal. To a certain extent this is also true in man, since many wounds and ulcerations become covered with normally pigmented epithelium in the process of healing. This is an indication that the regenerating epidermis carries with it regenerating pigment cells.

The source of epidermal cells in wound healing has been shown to be the epidermis of the periphery of the wound, the hair root sheath, the sebaceous gland duct, and the deeper portion of the eccrine sweat duct.[22-25] The epithelial cells of these areas actively migrate to cover the granulation tissue produced by the regenerative effort of the mesoderm. Mitotic activity is much more pronounced in the matrix zones at some distance from the border than in the migrating cells themselves.

Melanocytes, which are the normal prototypes of nevus cells, are found with epidermal cells and around the upper part of the follicular sheath. They are carried along or migrate with the rest of the epithelium. In wound healing of pigmented skin, clinical pigmentation often lags behind epithelization, and reappears first around hair follicles and at the periphery of the wound, spreading from there to cover the defect. This indicates that melanocytes not only migrate but multiply enough to reestablish their normal ratio in the regenerated epidermis.

Nevus cells, especially early in their development, when they are junctional and active, are also found with the basal cells of the epidermis and with the follicular sheath of the hair. It is to be expected that any nevus cells present in such areas, such-

as in a compound nevus which is removed for cosmetic purposes, would be carried along with the regenerating epithelium over the denuded area. In some cases they obviously multiply and form a new junctional nevus above the quiescent intradermal remnants of the old nevus.

The question of the prognostic significance of this process then arises—whether this means activation of a quiescent nevus, implying possible progression to a malignant state. There is no evidence of such implication in either Walton's or our material. Walton found that no junctional activity occurred in any nevus which did not show it in the original lesion. The two cases in our series in which the original nevus was available for study support this view. In none of our cases was there any evidence of the criteria upon which the diagnosis of malignancy in a cellular nevus rests.[26] There were no mitoses; there were no cells of unusual size, and there was no reactive inflammatory infiltrate.

It seems, instead, that the nevus relives an early part of its natural history. Just as in children the finding of a junction nevus is the common expected occurrence and does not imply malignant development, so here, in a young epidermis, nevus cells form junctional nests. It may be presumed from the experience of a great number of dermatologists polled in a recent survey,[2] that this process eventually would have reached a stage of balance and quiescence.

Our own experience in these and other cases and Walton's study would suggest that it is preferable to microscopically examine at least the superficial portion of nevi removed for cosmetic purposes. Such examination would allay any anxiety of the patient and enable recognition of the extremely rare nevus that shows histologic evidence of malignancy in spite of clinical quiescence as determined by an experienced dermatologist.

Summary

Two mechanisms of recurrence of common benign nevi after incomplete removal are described as follows: a regrowth of the tumor mass in a ring around the scar and a regrowth of a pigmented junctional nevus. Nineteen cases illustrating the latter mechanism are presented.

It is felt that the junctional nevus cells originate from the periphery and from hair root sheaths of the original lesion and regenerate in the same manner as the melanocytes of the regenerating epidermis.

It is felt that this mechanism of recurrence does not imply malignant potentiality.

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Pemphigus Vulgaris with Lesions of the Rectal Mucosa

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It is the purpose of this paper to report a case of pemphigus vulgaris with rectal lesions. Wiener [1] mentions in his text that specific lesions for pemphigus occasionally occur in the esophagus and rectum. However, we have been unable to uncover any cases similar to ours in the literature.

Report of a Case

A 48-year-old Jewish woman was first seen on an ambulatory basis on March 19, 1957, complaining of "painful raw areas" in the mouth. Examination revealed tender erythematous friable lesions with superficial denudation involving the lips, tongue, gums, palate, buccal mucosa, and, to a lesser extent, the pharynx and nasal mucous membranes. The ulcerations were most marked on the tongue, where a scalloped appearance of the edges was noted. The oral and nasal lesions were treated with hydrocortisone sprayed locally. Elixer of diphenhydramine (Benadryl) was used as a mouthwash before meals to reduce the discomfort. On March 24, 1957, five days later, the patient developed bullous lesions over the trunk, extremities, vulva, and perineum. These blisters were easily broken, and superficial denuded erythematous patches remained. The patient was otherwise generally in good health except for a recent weight loss related to the oral changes.

A biopsy of a small, presumably early, intact blister of the right thigh was made. Microscopic study showed an intraepidermal bulla, with epidermal separation just above the basal layer. There was definite acantholysis of epidermal cells. In addition there were some eosinophils and polymorphonuclear leukocytes in the blister cavity. The dermis showed a scattered infiltrate of eosinophils and, to a lesser extent, polymorphonuclear leukocytes.

The patient was hospitalized on March 26, 1957. Physical examination at that time was essentially normal, except for the lesions of the skin and mucous membranes previously described. The laboratory studies on admission, including a complete blood cell count, urinalysis, serologic test for syphilis, chest x-ray, ECG, and serum cholesterol, were normal. Past history revealed that she had had a subtotal thyroidectomy for hyperthyroidism many years previously and a myocardial infarction over a year prior to the onset of her present illness.

The patient was treated with 15 mg. of prednisone (Meticorten) every six hours. Potassium chloride therapy and other supportive measures were instituted in conjunction with the steroid treatment. Her blood pressure and weight were recorded daily. She improved rapidly, and the skin lesions were almost completely healed within four days. The mucous membrane lesions responded more slowly. On March 30, 1957, a vesicular conjunctivitis was noted. Local hydrocortisone therapy was instituted, and the lesions cleared in a few days.

The prednisone dosage was reduced gradually, and the patient continued to do well until April 6, 1957. At this time she developed a fever, with a temperature of from 101 F to 102 F, in conjunction with an exacerbation of the mucosal lesions. There was no indication of a superimposed infection. However, a blood cell count revealed a leukocytosis of 13,900 leukocytes, with 85% polymorphonuclear leukocytes. Blood, urine, and throat cultures were noncontributory, and a chest x-ray was normal. Oxytetracycline (Terramycin) was given orally without effect.

On April 9, 1957, corticotropin (ACTH) therapy (40 units intramuscularly per day) was started, in addition to the prednisone (70 mg. per day). The fever subsided rapidly, and the mucous membrane lesions began to heal. However, in the next 10 days she became manic. Fortunately, this psychological change was controlled with 100 mg. of chlorpromazine (Thorazine) per day without necessitating a drastic reduction in the steroid dosage.

She continued to improve until May 8, 1957, when she became depressed and a bit confused and developed diarrhea and incontinence of feces. Laboratory examinations of the serum sodium, potassium, CO_2-combining power, and the blood urea nitrogen were normal. The steroid dosage

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Fig. 1.—The denuded area of the left side of the tongue.

Fig. 2.—Erythematous denuded patches of the posterior palate area.

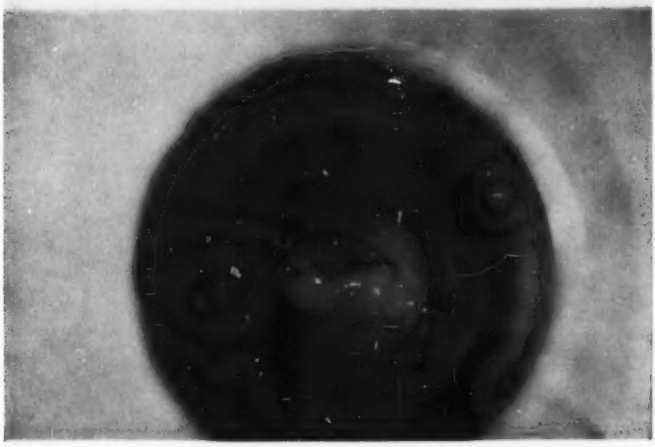

Fig. 3.—Anoscopic view of lower rectum showing edema, granularity, and bleb formation.

was reduced, and the chlorpromazine, discontinued. Within a few days she was again alert and was in better control of her anal sphincter. However, on May 19, 1957, she began passing large amounts of blood by rectum.

A proctologic examination was done by one of us (G. M. F.) on May 21, 1957, to determine the cause of the rectal bleeding. Externally there were a few small tags: digital examination revealed a hypertrophic papilla about 1 cm. in diameter in the right posterior area. Anoscopic examination disclosed moderate-sized internal hemorrhoids, with slight erosion. The proctoscopic findings were most unusual. The mucosa from the mucocutaneous line to the 13 cm. level was irregularly thickened and friable, with increased blood vessel markings. There were several scattered patches which resembled blebs, with definite edges, but which did not wipe away with gentle manipulation. The largest bleb was located at 10 cm. and was about 1 cm. in diameter. In several areas the mucosa was markedly heaped up, and on the surface of the ridges were numerous small pitted ulcerations. The lesions grossly resembled those present in the mouth.

The steroid dose was increased by 10 mg. of cortisone (the patient was receiving 5 mg. of cortisone and 35 mg. of prednisone at that time). The rectal bleeding stopped almost immediately. Four days later the rectum was reexamined for the purpose of taking color photographs and also to check the pathology after the increase in cortisone. The lesions had subsided to some extent, and the inflammatory edema was considerably lessened. The ulcerations had disappeared, but the blebs were still present.

The patient was discharged from the hospital on May 26, 1957. She has remained under control with mild oral mucous membrane activity with 35 mg. of prednisone and 15 mg. of cortisone to the present (June 20, 1957).

Comment

Pemphigus vulgaris is a severe dermatosis with grave prognostic implications. The presence of mucous membrane lesions, especially at the onset, has been felt to indicate a particularly malignant form of the disease.[2] With the advent of corticosteroid and corticotropin therapy, the outlook has become considerably brighter.[3-5]

Our patient presented acute diffuse oral mucous membrane involvement and subsequently developed a generalized bullous eruption. Biopsy of one of the skin lesions revealed an intraepidermal blister, with acantholysis of the epidermal cells. The process responded dramatically to the initial prednisone treatment. However, at one stage it was necessary to use high doses of corticotropin. At this point she developed a manic psychosis, and the question of reducing the steroid therapy became of pressing importance. Fortunately chlorpromazine was effective in controlling the psychological changes. It should be noted that chlorpromazine has been reported to produce hypokaliemia. This, of course, is of great importance to patients taking adrenal steroid treatment.[6]

A proctologic study was done because the patient began passing large amounts of blood by rectum. The examination revealed an irregular thickened friable mucosa, with what appeared to be bleb formation extending from the mucocutaneous line to the 13 cm. level. In addition there was "heaping up" and ulcer formation in the rectal mucosa. A biopsy was not done, because of the danger of increased bleeding and, possibly, bowel perforation. These changes responded rapidly to an increase in the corticosteroid dosage, thus ruling out an unusual reaction to the steroids. We believe that these bleb-like lesions of the rectal muscosa are specific for pemphigus vulgaris and are analogous to the blistering eruption of the skin and orificial mucous membranes.

In support of this concept, Stoughton has shown that thiol compounds, urea, and lithium bromide will cause separation of the gastrointestinal mucosa much in the same manner as epidermal cells exposed to these agents. This process in the skin produces a picture of acantholysis. Despite the fact that there are no known intracellular bridges in the intestinal epithelium the vesicle formation in each site appears to be on a similar basis, that is, loss of cohesiveness of the cells.[7]

Summary

A case of pemphigus vulgaris with rectal mucosa lesions is reported. The clinical

picture is described, and the process is discussed. We believe that these mucosal changes are analogous to the skin and orificial mucous membrane lesions and therefore are specific for this disease.

An extensive review of the literature has failed to disclose a description of specific lesions of the rectal mucosa in pemphigus vulgaris.

450 Sutter St.

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The Centenary of Dr. Fordyce

1858-1925

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Dr. John Addison Fordyce was born in Guernsey County, Ohio, Feb. 16, 1858. He received the A.B. degree from Adrian College, Adrian, Mich., in 1878 and his M.D. degree from Northwestern University Medical School (Chicago Medical College) in 1881. He then served a two-year internship at Cook County Hospital. From 1883 to 1886 he practiced general medicine in Hot Springs, Ark. The next three years (1886-1888, inclusive) he spent in the great medical centers of Vienna, Berlin, and Paris. In Vienna he studied dermatopathology with Kaposi; in Berlin he studied with Koch, Lassar, and Behrend, and in Paris he studied with Besnier, Vidal, and Fournier.

In 1888 he returned to the United States and established his residence and practice in the city of New York. For the next thirty-seven years (1888-1925) Dr. Fordyce was one of the most prolific writers and contributors to American dermatology. He was an inordinate worker. Perhaps his outstanding contribution to American dermatology was the role he played in developing one of the largest and best-equipped centers of dermatology and syphilology in America. This he accomplished at the College of Physicians and Surgeons, Columbia University, where he established one of the best postgraduate dermatologic centers in America. Dr. Fordyce thus trained more than one hundred fifty doctors in dermatology who today are leaders in various dermatologic centers of America.

Dr. Fordyce was not an orator, but he was a great teacher, for good teaching is not synonomous with oratory. Good teaching is often obtained by inspiration, by demonstration, by deeds, and by enthusiasm. Dr. Fordyce always recognized and applauded ability, ambition, and accomplishments in young men.

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John Addison Fordyce, M.D.

Dr. Fordyce described pseudocolloid of the lips (Fordyce disease) under the following title: A Peculiar Affection of the Mucous Membrane of the Lips and Oral Cavity (*J. Cutan. Dis.* 14:413, 1896). His name is also connected with Fox-Fordyce disease, chronic, itching papular eruption of the axillae and pubis (*J. Cutan. Dis.* 20:1, 1902).

In 1911 Fordyce published one of the earliest papers in American dermatologic

literature on allergy. In this paper he prophesied that "the question of anaphylaxis brought about by the use of horse serum, foods, or bacterial proteins is an exceedingly interesting one from a dermatologic standpoint and will probably render much clearer our understanding of many forms of skin reactions such as the erythema group, including purpuras and various types of eczema" (The Possible Influence of Anaphylaxis on Skin Reactions, *J. Cutan. Dis.* 29:129, 1911).

Dr. Fordyce had the ingredients of great leadership. He had patience, perserverance, ability, common sense, knowledge, vision, and fairness. Thus, when he died, in 1925, he had earned the respect, the admiration, and the love of all who knew him. Fordyce's contributions to American dermatology will live forever.

"A good life hath but few days, but a good name endureth forever."

Ecclesiasticus 41:13
(Ben Sira)

1 N. Pulaski Road (24).

Chondrodermatitis Nodularis Chronica Helicis

A Nondeforming Surgical Cure for Painful Nodule of the Ear

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Since the description of "painful nodule of the ear," by Foerster,[1] and "chondrodermatitis nodularis chronica helicis," by Winkler,[2] a multitude of treatments for this disease have been recommended. These include x-ray, radium, cryocautery, galvanocautery, fulguration and curettage, multiple injections of the area with procaine,[3] injections with hydrocortisone,[4] and, almost universally, surgical excision as the treatment of choice. These treatments have in common one or more of the following drawbacks:

1. High incidence of recurrence after treatment
   A. Recurrences in 88% (14 of 16) of patients treated by x-ray, radium, CO_2 snow, fulguration, and caustics[5]
   B. Recurrences in 18% (15 out of 84) of cases treated by excision, cured with second excision[5]
   C. Recurrences in 31% (18 out of 58) cases treated by "wide surgical excision,"[3] retreated with second, third, and fourth excision
2. Multiple therapeutic procedures needed
3. Permanent deformity of the treated area, with poor cosmetic end-result
4. Pain with treatment and/or after treatment.

The following surgical procedure has been used on 13 patients with 14 lesions. Eleven patients had lesions on the helix; one, on the antihelix, and one, on both helix and antihelix, ipsilateral. It has the following advantages:

1. Simplicity (great surgical skill not necessary)
2. Speed (no suturing necessary)
3. No residual pain and immediate relief of preoperative pain
4. No residual scarring or deformity
5. Only one therapeutic procedure necessary
6. Treatment based on physiologic rationale
7. Minimum sacrifice of normal tissue
8. No recurrences to date (four years after surgery).

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Pathologic Physiology of Chondrodermatitis

The skin over the helix, and to less extent over the antihelix, is peculiarly characterized by three factors which play a part in the pathogenesis of chondrodermatitis:

1. Exposure, as an unprotected rim, to the effects of trauma from
   A. Sunlight and frostbite
   B. Pressure from sleeping on ear, blows, etc.
   C. Earphones, coifs, headpieces, etc.
2. No subcutis to provide insulation, cushioning, or more adequate blood supply
3. Increased circulatory demands on the narrow strip of dermis by overlying epidermis and underlying perichondrium and elastic cartilage.

This operation was developed on the assumption that the basic pathologic changes are primarily in the cutis. They are secondary (if present at all) in the perichondrium, cartilage, or epidermis.[3,5] I postulated that these changes are the result of chronic scarring, from either actinic or mechanical trauma. This binds together the epidermis, cutis, and perichondrium into a firm unit. Additional trauma leads to edema in a "bound down" area, with resultant pressure-induced ischemia and possibly ischemic neuritis. "Poor blood supply," both preceding and following injury to the area, with its "tautly stretched epidermis," was mentioned by Newcomer et al.[3] and other investigators. Previous investigators did not suggest pressure ischemia as the basic cause.

Pain, often increased by pressure and by exposure to cold, has been reported by all previous investigators. It is grossly out of proportion to the intensity of the pain

present in most other inflammatory dermatologic lesions of similar size and severity. Ischemic lesions are notoriously painful. Buerger's disease, Raynaud's disease, erythermalgia, and hypertensive ulcers of the lower extremities due to arteriolar inadequacy are classical examples. Stasis lesions are not usually painful. This suggested that the "poor blood supply" was on an ischemic rather than a stasis basis.

Macroscopic and Microscopic Anatomy of the Helix Area

According to Maximow and Bloom, the lateral side of the ear is characterized by its complete lack of subcutaneous tissue. Its normal histologic structure is cutis directly attached to perichondrium over elastic cartilage.[6] Only the characteristic small blood vessels of the cutis are present. Both the large blood vessels and the insulating, cushioning, and shock-absorbing properties of the subcutis fat pad are lacking. This cutis is called upon to furnish itself, the overlying epidermis, and the underlying perichondrium and elastic cartilage with adequate circulation.[6] "Cartilage never possesses blood vessels of its own."[7] It is nourished only by diffusion of tissue fluids from the perichondrium. This area should be susceptible to slight impairment in its normally minimal circulation. The common finding of "cauliflower ear" and the ease with which ears are frozen indicate that it is. Consequently, advanced chondrodermatitis might be logically expected to show histologic evidence of secondary perichondritis and then of chondritis, as previously reported.*[3,5] If they are present, I believe these changes to be on a mechanical, pressure-induced ischemic basis, secondary to the changes in the cutis. Correction of the mechanical pressure factor should correct the ischemia. Correction of the ischemia should lead to healing, as in the treatment of other skin lesions of ischemic pathogenesis. Debridement of existing devitalized, abnormal, reactive, inflammatory tissue makes healing easier. It is consistent with good surgical practice.

Surgical Approach

The surgical approach has four aims:

1. To cut the old adhesions, which firmly bind down the epidermis and cutis on the perichondrium
2. To eliminate the mechanical "squeezing" of the dermis between perichondrium and epidermis, leading to ischemic change
3. To remove existing reactive inflammatory tissue in the cutis, perichondrium, cartilage, and epidermis at the chondrodermatitis site
4. To cut the sensory nerves supplying the area, for immediate relief of the characteristic pain.

Surgical Technique

Two to five cubic centimeters of 1% procaine † is injected into the skin of the scapha just below the chondrodermatitis lesion. More is injected into the posterior rim of the helix, medial to the lesion. This balloons widely the skin over and around the area of chondrodermatitis (Fig. 2). This ballooning makes for an avascular operative field and, by hydraulic pressure dissection, breaks up connective tissue scar adhesions to the perichondrium. In grossly thickening the operative area, it obliterates the 90 degree reflection of the skin from the helix into the scapha on the lateral ear. This makes the ensuing dissection easy and quick.

As soon as the local anesthesia from the procaine has become effective, a 2 or 3 mm. specimen around and including the main area of chondrodermatitis is punched deep enough that the underlying cartilage is felt with the punch. The punch is inserted perpendicular to the side of the head. This punch specimen is removed, and the depths of the wound are then stained with

* It should be noted that Newcomer et al.[8] found similar changes in perichondrium and cartilage in a large series of normal ear specimens taken from cadavers of patients over 40 years old.

† No hyaluronidase is used in the procaine, since hyaluronidase diffuses the procaine and interferes with hydraulic dissection. No epinephrine is used, because of the acral location of the surgery, because of already inadequate circulation in the area, because the hydraulic pressure alone produces a relatively avascular field, and because the reactive hyperemia occurring after epinephrine has worn off might induce bleeding after the patient has left the office.

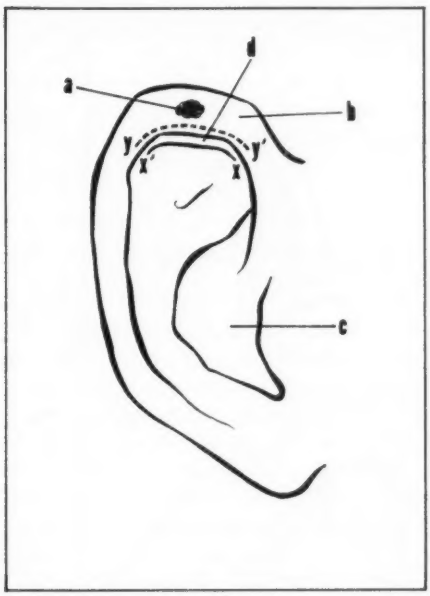

Fig. 1.—(*a*) Chondrodermatitis site; (*b*) helix; (*c*) cavum conchae; (*d*) scapha; *xx'*, incision, lateral side of ear; *yy'*, incision, medial side of ear.

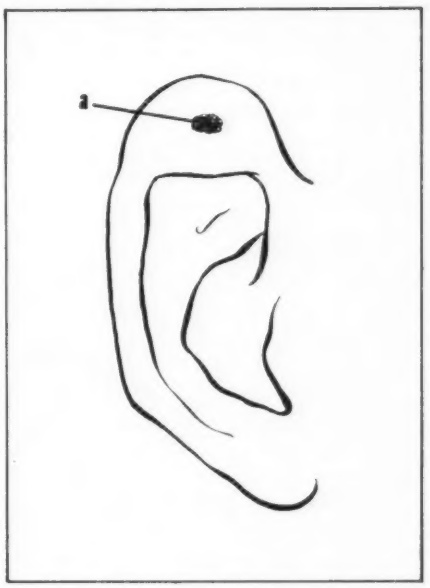

Fig. 2.—Diagram of ear into which procaine has been injected, showing ballooning of skin around chondrodermatitis site (*a*), with obliteration of helicoscaphal angle.

methylrosaniline chloride (gentian violet) on an applicator stick. The stain provides a landmark for position identification both on cartilage and on cutis. A curved incision, about 4 cm. long, is made through the skin on the lateral surface of the ear, down to the perichondrium. This incision is 7 to 12 mm. below the rim of the helix, following along, and just above, the promontory junction of the scapha and antihelix (*xx'*, Fig. 1). A similar curved incision is made on the medial side of the ear, 7 to 12 mm. down from the rim of the helix (*yy'*, Fig. 1). Both incisions are parallel to, and equidistant from, the helix rim.

The skin is then retracted with skin hooks, and by sharp dissection it is freed from the underlying perichondrium, to separate and free the ribbon of skin over the helix between the two parallel curved incisions (Fig. 3). Once this ribbon of skin has been dissected completely free, it is grasped in the fingers of both hands and gently stretched several times by the surgeon. A very appreciable elongation will result from this. Skin hooks are then slipped beneath the attached ends of the "ribbon," and it is lifted as high as possible, to allow visual inspection of the underlying cartilage. By sharp dissection, a shallow crescent-shaped slice of cartilage, about 1.5 to 2 cm. long, is then taken off the lateral rim of the helix (Figs. 3*a* and 3*b*). This is about 3 to 6 mm. wide over the point of chondrodermatitis.‡ The blue stain made by the methylrosaniline chloride ensures accurate centering of the crescent.

The cartilage excision is shallowed out to nothing at each end (Fig. 3*a*), about 1 cm. peripheral to the site of chondrodermatitis. After the cartilage removal, the center of the ribbon of skin is twisted, and its dermal side is exposed. Any firm reactive tissue

‡ This cartilage excision is not off the top of the helix but off the lateral rim (Fig. 3*b*). The helical rim is formed by a 90 degree fold in the auricular cartilage and is perpendicular to the plane of the ear and head.

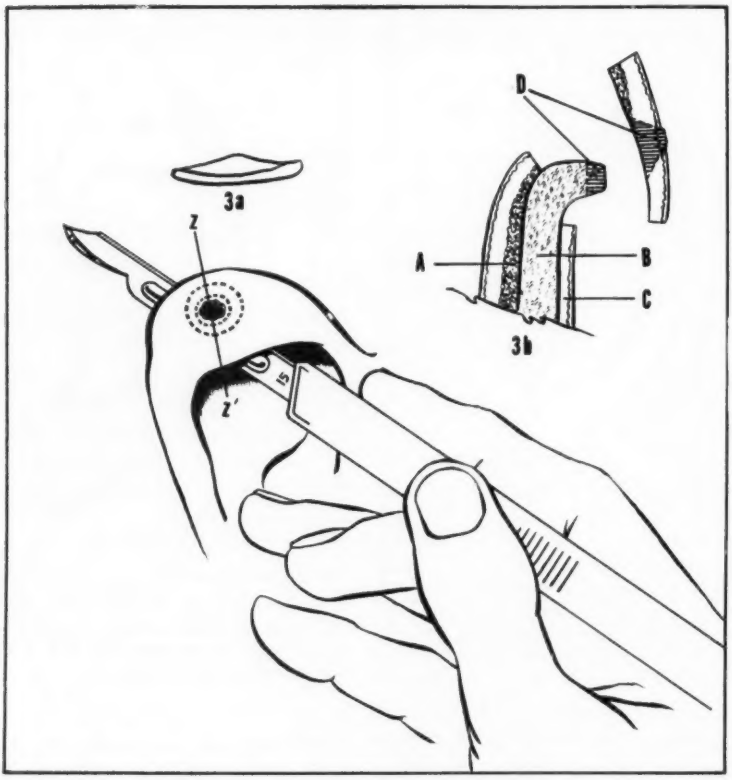

Fig. 3.—Ear with incisions, lateral and medial, connected and scalpel lifting away the free ribbon of skin over the helical cartilage. Outside dotted lines around chondrodermatitis lesion indicate shallow beginning of scoop-out of cutis. Inside dotted lines show when it is through the epidermis. A magnified cross section to show the tissue relationships through *ZZ'* is presented in Figure 3*b*. Subcutaneous fat tissue (*A*) is present on the medial side of the ear between cutis and cartilage (*B*) but is absent on the lateral side, where cutis (*C*) binds directly to the perichondrium. The lined areas (*D*) illustrate the cartilage and cutis areas excised. Fig. 3*a* is a magnified drawing of the cartilage wedge to be removed.

palpable is excised free from the dermal side, almost to the epidermis, at the site of the methylrosaniline chloride-stained "punch out" of the chondrodermatitis by a single sloping-bordered "scoop" of the scalpel (Fig. 3*b*). This can be submitted for biopsy, along with the punched specimen, if the surgeon is in doubt as to diagnosis.

The operation completed, the dermal surface of the ribbon of skin is dusted with thrombin powder and then "glued" into its normal position on the helix cartilage. Two-inch gauze squares are set in the supraauricular notch and on the external upper ear against sheets of Telfa (combined fabric and plastic bandage) placed over each incision. A 3 cm. thick, pressure-protective pad of 2 in. gauze squares is set over the cavum conchae. All these gauze squares are fixed to the head with gauze wraps, with use of moderate pressure. The pressure prevents postoperative bleeding and the formation of "dead space." Forty-eight hours later, the dressings are removed and the ear is inspected for hematoma. If this is present, it is evacuated through the incision by gentle pressure and the surgical site is again covered by a pressure dressing.

If there is no hematoma, a 2 cm. thick pad of gauze sponge is applied over the lower ear and a 3 cm. pad is applied below the temporoparietal junction above the ear to protect the operated-on area from inadvertent pressure. This is left on for five days, after which time all dressings are removed.

It should be noted that this operation is done as atraumatically as possible. No tissue is devitalized by being handled with rat-toothed forceps or by blunt dissection. All existing devitalized, inflamed, abnormal tissue is removed. Not enough cartilage is excised to be noticeable postoperatively. However, the shallow wedge removed is enough to relieve future pressure on the involved area, when accompanied by elimination of old adhesions, stretching of the overlying tissue, and excision of abnormal tissue.

No visible deformity follows healing, since the only visible incision (on the lateral side of the ear) heals as a hairline scar hidden in the shadow of the scapha. The operation sounds rather complicated as described. It can be done in less time than it takes to read about it.

Complications

No complications have been noted in any of the 13 cases thus treated, with the following exceptions. One patient had a small hematoma present on the lateral side of the ear, below the helix rim, on the second postoperative day. This was evacuated through the incision, and the area was dusted with thrombin powder. Healing was uneventful. In one patient, the incision site oozed postoperatively for several hours, although no hematoma formed. He was given an aqueous solution of oxalic and malonic acids (Koagamin), 2 cc., intramuscularly, and the area was reopened and dusted with thrombin powder. Healing was uneventful.§ The paroxysmal pain characteristic of most cases of chondrodermatitis was present in 11 of our 13 patients and stopped immediately after surgery. No postsurgical chondritis developed in any case, and no secondary infection was seen.

§ The routine use of thrombin powder as "physiologic glue" was done in the last nine cases, as outlined. These two cases were in the first four.

Summary

Chondrodermatitis is postulated to be the result of mechanical pressure from edema in an area of adhesions from old traumatic scarring. This produces ischemia, with possible associated ischemic neuritis, in an area (usually the helix) where local demands on the circulation are high, available circulation is low, and incidence of trauma is great. An operation is described which (1) eliminates the mechanical squeezing of the cutis which caused the pathologic changes, by mechanically stretching the cutis and epidermis, after dissecting them free from the underlying perichondrium, and cutting old adhesions; (2) surgically excises existing pathologic tissue in cutis and epidermis; (3) cuts the nerves to the area for immediate relief of pain, and (4) removes the projecting rim of helical cartilage.

This procedure is easy and quick, and it leaves no postoperative deformity. It gives immediate pain relief, is done in one operation, and has given no recurrences.

The illustrations in this article were made and contributed by Mr. Wilson G. Turner, of Whittier, Calif.

301 E. Hadley St.

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Hyposensitization Against Rhus Dermatitis

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This paper deals with immunologic prophylaxis of Rhus dermatitis due to Rhus radicans (poison ivy) and Rhus toxicodendron (poison oak). A comprehensive summary of the clinical biology of Rhus dermatitis has been given in a previous paper, which forms the prelude to the present theme.[1]

A striking feature of the literature on Rhus prophylaxis is the contradictory nature of many reports. Students of the subject hold diametrically opposed views. Some achieve remarkable results which are just as remarkably denied by others. Despite genuine advances in the basic knowledge of allergic contact dermatitis, the issue of hyposensitization is one in which there is no end of clinical testimony but relatively little in the way of objective research. Therapeutic ambitiousness has colored the picture with extravagant claims.

The paramount aim of the present effort is to test the soundness of the concept of hyposensitization and to establish its biological characteristics. The practical application of this knowledge is for the moment a secondary issue.

The American Indian had the earliest experience with Rhus dermatitis. It is appropriate that he should have been the first to try to do something about preventing it. To this day the practice of chewing poison ivy leaves in the springtime persists among Indian tribes of the Southwest. That any benefit resulted is questionable. Perhaps the rationale was magical. The piquant fact, however, is that all subsequent attempts at hyposensitization have utilized the same principle, namely the administration of the plant or plant products. The earliest medical note is by Dakin,[2] in 1829. One surmises a healthy skepticism from the wording. "Some good meaning, mystical, marvellous, physicians, or favored ladies with knowledge inherent say the bane will prove the best antidote and hence advise the forbidden leaves to be eaten, both as a preventive and cure to the external disease." The modern era began around 1920 with the highly enthusiastic reports of Schamberg[3] and Strickler,[4] who gave plant extracts orally and by injection, with uniformly good results, both for prophylaxis and treatment of the acute dermatitis. The latter use is irrational and hazardous.[1] On the advice of leading dermatologists Rhus extracts for hyposensitization were included in New and Nonofficial Remedies in 1926. It is noteworthy, therefore, that 20 years later the Council on Pharmacy and Chemistry of the American Medical Association reviewed a mass of preponderantly favorable reports but could not decide whether hyposensitization was really worth while.[5] This issue continues *sub judice* to this very day.

Measurement of Hyposensitization

It should be made clear at the outset that I am concerned here with immunologic hyposensitization and not with nonspecific states of tolerance which can sometimes be achieved through graduated exposures to noxious substances. Furthermore, the central problem is not the prevention of sensitization but its weakening in an already sensitized person. Throughout this paper the term desensitization means clinical un-

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reactivity to fresh leaves. It implies solid immunity to Rhus dermatitis under average conditions of exposure. Hyposensitization refers to a decreased sensitivity which, when great enough, may provide partial degrees of clinical resistance.

Quantitation is the great resolver of dispute. In the present case, pre- and post-quantitative patch testings provide the only reasonably well-controlled means of estimating whether a change in sensitivity has occurred. Few have bothered with this chore. Uncontrolled clinical studies form the bulk of the evidence.

Unless the experimenter has a great many subjects, field studies in which the incidence of subsequent dermatitis in a treated and in an untreated group is compared are apt to be misleading. False claims have arisen from such "controlled" studies. The difficulty resides in the inability to control the variables. The following are a few of the difficulties. The exact degree of exposure is never known—mild dermatitis may be due to a mild exposure and not to hyposensitization. On the other hand, severe exposure may overwhelm a moderate degree of acquired resistance. Heat and sweating intensify the dermatitis. Mere contact is not enough; the leaves must be bruised to release the sap. The leaves get tougher and harder to bruise later in the year. Patients become more wary after springtime, the time of peak incidence. Accordingly, susceptible persons are rarely able to interpret their post-treatment experience accurately. The disorder often seems capricious; consequently many myths have arisen.[1] Zisserman and Birch's[6] report illustrates how easily misinterpretations arise. Nine hundred sixteen boys were followed who developed Rhus dermatitis at a summer camp where poison ivy plants flourished. They were surprised to find that under the same conditions less than half of these got the dermatitis the following season. They apparently did not consider the likely correct explanation, namely, lack of appropriate exposure. Instead they favored two improbable hypotheses: rapid loss of susceptibility or a great seasonal variation in the allergenicity of the plants.

Similarly after "treatments," some of which have been of very trivial nature, patients who escape the dermatitis are prone to consider themselves successfully immunized, rather than to entertain the possibility of inadequate exposure.

In contrast to the complexities of field study, the patch test provides an objective criterion of a change in sensitivity. Actually, it is not a "test" at all. It is the disease in miniature, essentially reproduced as it occurs naturally.

The pure synthetic allergen, 3-*n*-pentadecylcatechol (PDC), a stable crystalline material, has been used for patch testing throughout this study. It was applied in acetone solution by the previously described technique of open patch testing in a tenfold dilution series as follows: 1:100; 1:1000; 1:10,000; 1:100,000, and 1:1,000,000. It has been shown that the sensitivity titer, the greatest dilution still giving a visible reaction, is the most meaningful measure of the degree or depth of sensitization.[1] It is futile to expect absolutely reproducible results with biological testing of this kind. The method is crude and not highly sensitive.[1] Despite these limitations, and others which will become apparent later, much can be learned when the inherent range of error is fully appreciated. For practical purposes, conceding some unavoidable fluctuations and an early rise in some cases, repeated quantitative patch testing at intervals exceeding six weeks does not appreciably change the sensitivity of highly susceptible subjects.

The previous study brought out that the oleoresin generally gave higher titers than PDC in quantitative patch testing.[1] This is inconsistent, however. Even more noteworthy is the tendency for the oleoresin to produce more vesicular and intense reactions, especially with the higher concentrations. When the titers are indistinguishable, the oleoresin generally shows itself by this

stronger vesicular dermatitis. Allowing for these differences, it was found that patch testing with oleoresin gave results comparable to PDC after hyposensitization.

Rubbing fresh leaves over the skin provided an excessive exposure. Violent reactions ensued in the highly sensitive subject which obscured real changes in the level of sensitivity. Usually the poison ivy victim contacts the plant casually and only minute quantities of sap are deposited. Crushing the leaf on the skin is not realistic. There is the further difficulty of standardizing leaf tests. Nonetheless, valuable information was gained by using a "finger-leaf" test along with quantitative patch testing. The index finger of a nonsensitive person previously contaminated with leaf sap is applied firmly to the skin for five seconds, without rubbing or twisting. It should be emphasized that even this method is far severer than casual exposure. Covering the exposure site did not always prevent the dermatitis from developing elsewhere.

More than 2000 subjects participated in this study.* These were drawn from prisons, mental institutions, the Army, and the general population. The age range was 4 to 70. All degrees of allergic reactivity were represented, from the subclinical to the exquisitely sensitive. About 90% were males. Over a three-year period many different schemes of hyposensitization were tried, with many false starts, detours, and blind alleys. The plan of attack frequently shifted as new insights developed. I have found it impossible to compress this wandering experience into the cold formality of charts, figures, and graphs. The raw data are mountainous. To preserve intelligibility I shall present only the significant residue.

Placebo Hyposensitization

It is highly instructive to examine the subjective clinical results of placebo prophylaxis. The fallaciousness of uncontrolled field studies is revealed in a most striking manner. Eighteen highly sensitive volunteers from the general population were given 8 to 10 weekly 1.0 ml. intramuscular injections of sesame oil. While the "post-treatment" patch tests showed no decline in sensitivity, 16 of these subjects expressed high satisfaction! These subjects entered the experiment in the hope of obtaining relief from severe, sometimes incapacitating Rhus dermatitis. For the first time in years, seven had no dermatitis at all and nine had trivial eruptions. They freely advertised this miracle to their friends, who thereupon swelled the experimental roster. Only two received no benefit.

The explanation of this astonishing result is not obvious. It is obvious that they were not contacting poison ivy sap, although some insisted that they could handle or walk through the plants with impunity. Perhaps they unconsciously took greater care once they had gone so far as to allow themselves to be discomforted by weekly injections. The desire of many subjects to please the investigator is another possible factor.

Patient satisfaction is not a reliable measure of efficacy. Inert materials give good clinical results in a high proportion. The history of the prophylaxis and treatment of Rhus dermatitis is a cogent example of the fact that patients, and often physicians, cannot recognize the useless, irrational, or harmful.[1] If most accounts could be taken at face value, traces of Rhus antigen afford remarkable protection. Indeed, it would now appear that the beneficient properties of this powerful material are not strictly confined to Rhus allergy. Its administration to patients with a variety of immunologically distant allergic disorders, such as asthma, allergic rhinitis, drug reactions, and chronic eczema, cured or improved over 75%![7]

Prophylaxis by Intramuscular Injections of Rhus Oleoresin

The oleoresin is the oily residue after evaporation of lipoid-solvent extracts of the

* Dr. William Epstein and Joseph Corcoran of this department provided technical assistance in many aspects of this study.

plant. It is a crude substance, the major portion of which is immunologically inert and nonallergenic.[8] Its potency and stability may vary considerably.[9] Many more papers have been devoted to intramuscular than to oral prophylaxis. The usual commercial intramuscular preparation consists of a 0.1% (1:1000) solution of the oleoresin in a vegetable oil (corn, peanut, or sesame). Alcohol has been used as a solvent, but it produces too much pain. The instructions generally call for two to four 1.0 ml. injections. It should be emphasized that 1 ml. contains 1 mg. of oleoresin by weight. Some students advocate a few more injections and sometimes slightly higher concentrations. Clarke and Hanna's [10] summary, in 1942, reported that 16 of 18 previous prophylactic studies yielded more than 50% good results. Splendid success was recorded by many. Gowen's results are indeed remarkable.[11] One or two injections provided a firm immunity which lasted two to five years! In a "controlled" field study Blank and Coca [12] found brief prophylaxis extraordinarily effective. Sixty-six per cent of an untreated control group got Rhus dermatitis, as contrasted to twenty per cent treated with four 0.5 ml. injections of 0.2% oleoresin. With twice this quantity (four 1.0 ml. injections) only 7% were afflicted. The following statement from their paper is revealing. "The first method of study [that is quantitative patch tests] was found strangely enough not to be available, because the result of quantitative skin tests was the same after desensitization injections as before." Similarly, Spain and Cooke remark: "Since the result clinically was successful, it must be concluded that the degree of immunity developed by treatment cannot be determined by any change in the cutaneous reaction." [13]

Clarke and Hanna [10] gave five-minute subcutaneous injections and obtained impressive results, 56 of a group of 82 escaping the dermatitis completely. With a series of small injections, Caulfeild accomplished good prophylaxis, accompanied by a decline in the patch-test reaction.[14,15] Molitch and Poliakoff gave a series of injections and obtained "all or none" results—every control subject, but none among those treated, got Rhus dermatitis![16,17]

In summary, the protagonists of intramuscular oleoresin prophylaxis have claimed benefits with extraordinarily small amounts of allergen, usually less than 5 mg. and rarely as much as 20 mg. Others have denied these claims.[6,18-22] Foremost among these is Shelmire, whose contributions to this field have been sizable. He early abandoned injection methods, estimating that it would take at least two hundred 1 ml. injections of 1.0% oleoresin to effect hyposensitization.[23] He found four injections of commercial-type extract worthless. Apropos of this, Howell [24] and I [1] found many of these extracts completely inert. Indeed, Shelmire noted no change in sensitivity with 30 or more injections.[25] Greenberg and Mallozzi's study [21] is documented with quantitative patch tests; two injections did not change the sensitivity. They inveigh against those who dismiss the significance of patch testing.

It is interesting that the prophylaxis controversy extends even to animal studies, wherein greater control is possible. Again the positions are extreme: Ginsberg et al.[26] observed no effect when oleoresin was injected into Rhus-sensitized guinea pigs in accordance with the dosage prescribed for humans. Contrariwise, with a half dozen injections Stratton produced complete immunity lasting at least six months.[27] Mason and Lada [28] went even further and reported that the prior injection of pentadecylcatechol-albumin conjugate could prevent contact sensitization. In my opinion, this is improbable. In humans, prior feeding or intramuscular injection of substantial amounts of pentadecylcatechol had no influence on the capacity to become sensitized.[1]

Current Study of Intramuscular Prophylaxis with Oleoresins

The results will be given in synoptic form, leaving questions of toxicity, dosage

schedules, and other matters for later discussion. The material used was oleoresin in sesame oil. Its high potency was verified by its capacity to produce a dermatitis in highly sensitive persons with a volumetric dilution of 1:1,000,000 in acetone.

Four 1 ml. weekly intramuscular injections of 1:1000 oleoresin in sesame oil produced no change in the quantitative patch-test sensitivity of eight moderately sensitive subjects. In the same subjects, 14 weekly injections were likewise without any effect. Thereupon a graded series of weekly injections beginning with 0.1 ml. of 1:10,000 oleoresin and reaching a maximal amount of 1 ml. of 1:10 oleoresin was given to a panel of 17 moderately sensitive prisoners capable of reacting to 1:100,000 PDC. The 1.0 ml. weekly injections of 10% oleoresin were continued to the termination of the study. The progression of doses was changed as demanded by individual intolerance. Obviously, the total periods required to reach a given quantity varied greatly. Quantitative patch tests were done every eight weeks. The threshold amounts that produced a rather definite change in the sensitivity of most subjects, ignoring inherent variability of the method, was of the order of 600 to 800 mg. Maximum hyposensitization required 2000 to 2500 mg. This took five to nine months and never less than 22 injections. These figures are no more than general approximations. Attention is called to marked differences in individual responses. No subject was unaffected, but some were less responsive than others and did not achieve the same final resistance, even though the members of the group seemed to have about the same degree of sensitivity originally. Only one person became completely immune to leaves. The "finger-leaf" test still produced dermatitis in the other 16. The continued injection of 10% oleoresin up to a total of 4000 mg. did not appreciably reduce the sensitivity further than with 2500 mg. These results bear out Shelmire's contention that intramuscular prophylaxis is exceedingly difficult. It is also evident that there is an upper limit beyond which no reasonable amount has any further hyposensitizing effect.

Intramuscular Prophylaxis with Pentadecylcatechol

The major portion of this project was concerned with the utilization of 3-*n*-pentadecylcatechol † for prophylaxis. The desirability of using this chemically defined stable substance became obvious after Dawson and his collaborators [29] accomplished its synthesis. Originally intramuscular administration seemed preferable, but this view had later to be changed. As a consequence of this false presumption, over 1000 subjects were subjected to intramuscular injections. The allergen was dissolved in sesame oil. Two per cent aluminum monostearate was added, with the hope of increasing the repository effect. It was found that acetone extracts of guinea pig muscle which had received injections of 1 ml. of 10% PDC three to four weeks previously gave sharp patch-test reactions in highly sensitive subjects. This proved that some allergen was still present after a month. The oil sometimes seemed encapsulated in a pocket and oozed out of the cut muscles at the time of killing; occasionally an abscess formed. Innumerable dosage schemes and concentrations were tried, ending finally in the practice of giving graduated weekly doses of 10% PDC, beginning with 0.05 ml. All the subjects were clinically The pilot studies were done on 46 prisoners sensitive to leaves; all degrees of sensitivity from mild to extreme were encompassed. patch-tested every eight weeks. A summary of the entire experience follows.

The threshold amount producing an unmistakable reduction in sensitivity was in the range of 800 to 1100 mg. Maximal effects were obtained with 2500 to 3000 mg.

† Crystalline PDC was initially supplied by Dr. Dawson of Columbia University. Subsequently, the Lederle Laboratories Division, American Cyanamid Company, furnished it in generous quantities.

Larger quantities were without benefit. Again these are generalizations which bypass much individual variation. A larger amount of PDC than oleoresin was required for maximal hyposensitization. This difference is probably attributable to the presence of biologically more potent unsaturated allergens in the latter. Apart from the necessity of giving larger quantities of PDC to accomplish the same final state of hyposensitization, the experience with this substance was in all essential respects comparable to the use of oleoresin, and little more need be said of it. Hyposensitization was found to be a function of the total dose, not of the frequency of injections, within the assayed limits. It made little difference whether the injections were given every 4, 7, or 14 days. In no instance was complete desensitization accomplished in persons of high sensitivity. This seems impossible of attainment with current materials and methods of intramuscular prophylaxis.

The highest practical intramuscular dose is 1 ml. of the 10% concentration. Many subjects received 2 and even 3 ml. injections in the final stages of hyposensitization, but local discomfort and other adverse reactions were prohibitive.

Four subjects with mild leaf sensitivity were given 250 mg. (2.5 ml.) once weekly for four weeks (1000 mg. total). Local pain and tenderness were great; three developed exanthematous rashes. All were "sick," with varying degrees of fever, malaise, weakness, and other signs of systemic disturbance. The impression was gained from this "crash" prophylaxis that the hyposensitizing effect was somewhat less than if the same amount had been given in gradually ascending doses. Obvious reservations attach to this estimate in view of the unusual circumstances; moreover, 1000 mg. is just about the threshold amount. At any rate, my original thought that huge amounts given in a brief time might "shock" the subjects into unreactivity was not sustained.

Intramuscular Prophylaxis with Alum-Precipitated Pyridine Extracts of Poison Ivy Plants

Strauss and Spain extracted poison ivy plants with pyridine precipitated with alum and suspended the precipitate in saline solution.[30] The advantages of an aqueous suspension over an oily solution were claimed to be greater efficacy and lower toxicity, presumably because of slower absorption. They obtained good results with five preseasonal injections as compared with their previous failure with injection of alcoholic extracts. Recent studies are confirmatory and accompanied by warm endorsements.[31] Gaillard[32] considered that the immunity might last as long as three years. Passenger et al.[33] obtained 93% excellent or good clinical results in a series of 121 cases with five weekly injections as follows: (1) 0.3 ml. of 1:50; (2) 0.5 ml. of 1:50; (3) 0.7 ml. of 1:50; (4) 0.2 ml. of 1:5; (5) 0.5 ml. of 1:5; (6) 0.6 ml. of 1:5.

Current Studies with Alum-Precipitated Pyridine Extracts ‡

Six moderately sensitive persons received six injections according to the scheme of Passenger et al. There was no change in the sensitivity. With the same dosage, the same lack of effectiveness was demonstrated in another five mildly sensitive patients (1:10,000 PDC titers); thereupon, five highly sensitive subjects received six 1 ml. weekly injections of the highest strength material, 1:5. The sensitivity was not altered. Three highly sensitive persons received ten 1 ml. weekly injections of 1:5 extract. This is considerably more than the recommended total dose. There was no effect. The lack of toxicity emphasized by Passenger et al.[33] was confirmed. There was no adverse reaction even when the first dose was 1 ml. of the 1:5 concentration. A similar dosage of 1:5 oleoresin or PDC would have produced violent reactions. The issue,

‡ The material used in this study was Aqua-Ivy, furnished by Allergens, Division of Chemical Specialties Co., Inc., New York.

of course, is not lack of toxicity but effectiveness. Patch tests with 1:5 Aqua-Ivy on four highly sensitive subjects produced no reaction. The material appears to be biologically inert. Presumably, its champions would hold that it becomes transformed into an active form in the tissues. There was no evidence of this. It is highly improbable that a substance incapable of producing a dermatitis can be useful for hyposensitization.

Oral Prophylaxis with Oleoresin

From the very start Shelmire recognized the impossibility of achieving hyposensitization with minute amounts of allergen. He has insisted that for persons of average sensitivity 2000 mg. of oleoresin is required orally.[23] A true decline in sensitivity was demonstrated by quantitative patch testing and by controlled clinical exposures. Furthermore, he warned against promising too much, stating that reduction of sensitivity to the subclinical level, not complete desensitization, was the practical goal. His method consists of having the patient ingest, by dropwise ascending doses, one 30 ml. bottle of each of the following concentrations of the oleoresin in corn oil: 1:100, 1:50, and 1:25 (total, 2000 mg.). The drops are placed in capsules to avoid stomatitis. According to individual tolerance, three to nine months are needed for hyposensitization.

Students of oral prophylactic methods have been fewer but, for some reason, decidedly more critical. Gold and Masucci[34] advocated large total amounts given in the form of tablets (highest dose 150 mg. daily for 25 days). They were doubtless overenthusiastic in claiming complete or almost complete protection for a majority of 20 subjects who rubbed themselves with plants which the subjects themselves uprooted. Stratton[35] found oral prophylaxis more effective than the usual intramuscular routine.

Current Studies of Oral Prophylaxis with Oleoresin

Nine prisoners were studied carefully. Four were moderately sensitive, reacting to 1:100,000 PDC; three had 1:10,000 titers, and two were subclinical reactors, with 1:100 titers. Quantitative patch tests were repeated at eight-week intervals. The initial dose consisted of 1 drop of 0.5% oleoresin in sesame oil, and this was gradually worked up to a maximum of 15 drops of 10% oleoresin daily. The oil was dropped on the tongue and immediately swallowed with a glass of water. Quite definite changes in the sensitivity became apparent at about 1000 to 1200 mg. Maximal hyposensitization generally required 2500 to 3000 mg. Higher amounts (up to 4000 mg.) accomplished little more. These findings can be considered to have a reasonably good correlation with Shelmire's figure of 2000 mg. for the person of average sensitivity. None of the four moderately sensitive persons in this group became completely immune to leaves. For equivalent effects, larger amounts of oleoresin are required orally than intramuscularly. The final result is the same. Sustained release is probably the major factor in the superior efficiency of the intramuscular route. Besides, orally there may be some inactivation and imperfect absorption.

Oral Prophylaxis with PDC

About 500 subjects of all degrees of sensitivity participated. A pilot study in 16 prisoners with quantitative patch testing every eight weeks yielded the firmest data. The crystals were dissolved in either oil or alcohol and given by ascending dropwise doses, to a maximum of 100 mg. daily.

Significant changes in sensitivity occurred after 1500 to 1800 mg. Maximum hyposensitization required 3500 to 4000 mg. Up to 6000 mg. was given without any further effect.

Whether given orally or intramuscularly more PDC than oleoresin is required for maximal hyposensitization. PDC is the

Comparison of Effectiveness of PDC and Oleoresin Administered Orally and Intramuscularly

	Oral, Mg.	Intramuscular, Mg.
PDC	3,500–4,000	2,500–3,000
Oleoresin	2,500–3,000	2,000–2,500

least potent of the four natural poison ivy allergens, but it should be understood that PDC is not less effective than the oleoresin. More of it is required, but the final effect is the same.

Comparative Effectiveness

A rough measure of the comparative effectiveness of the oleoresin and PDC by oral and intramuscular routes is indicated by the amounts required for maximal hyposensitization as shown in the Table.

These figures are rough averages. They emphasize that the oleoresin is more potent, probably because of its unsaturated components. The hyposensitizing efficiency of the oleoresin is even higher than these figures reveal if it is considered that the allergenic constituents of this crude material account for less than 50%. In any case it is obvious that huge amounts are required, whatever the allergen or route. Hyposensitization in allergic contact dermatitis is by no means an easy matter. Similarly, in tuberculin sensitivity, the prototype of delayed-type allergy of which contact allergy is a member, a true decline in sensitivity requires an enormous number of injections of tuberculin. These hyposensitization difficulties in "delayed allergy" stand in contrast to certain forms of "immediate allergy," such as atopy, wherein rather small amounts of allergen may give clinical protection (without necessarily changing the skin reaction).

Hyposensitization by Intradermal Injection

Unlike oral or intramuscular prophylaxis, intradermal injection means putting the allergen into the shock tissue itself. Dilute solutions must be used to avoid excessive local reactions.

The following study was highly limited in scope and of a merely preliminary nature. Five moderately sensitive subjects received a total of six 0.25 ml. injections of 0.001% PDC in sesame oil intradermally once a week. Persistent, mildly inflammatory nodules developed at the injection sites on the forearm. Sesame oil alone did not produce inflammation. There was no change in the quantitative patch tests at the end of eight weeks. It should be realized that each subject received less than a total of 1 mg., a trivial quantity. This route probably has no future.§

Topical Hyposensitization

The phenomenon of "hardening" indicates that continued external contact to an allergen may eventuate in resistance to exposures formerly productive of a dermatitis. Knowledge of the subject derives mostly from observations on workers in chemical industries. From his huge industrial experience, Schwartz [36] is convinced that hardening occurs, and he supports his view compellingly with much circumstantial evidence. Hardening may be viewed as a form of topical hyposensitization. Jadassohn [37] first used the term and thought it a nonspecific (that is, nonimmunologic) phenomenon. Peck et al.[38] have compiled additional supporting evidence from many industrial sources. It is strange then, in the face of so much experience, that others should deny or question the phenomenon.[39,40] As is usual in such arguments, it is the want of controlled experimentation upon which ambiguities thrive. The temporary loss of sensitivity following a severe allergic contact dermatitis will not be considered herein as an instance of hardening. Information on this latter subject is meager.[1]

§ In a recent paper Keil claimed effective prophylaxis by the 'wheal' method using a course consisting of six weekly injections of 0.2 ml. of 0.001% PDC in peanut oil, almost exactly the same method which I have found useless" (Keil, H.: Prophylactic Treatment of Poison Ivy Dermatitis with 3-m-Pentadecyl Catechol Using the Wheal Method, New York J. Med. 58:57, 1958.)

Maisel [41] claimed hyposensitization by a most unique method in a single case. A scout leader severely troubled by Rhus dermatitis was not benefited by oral prophylaxis. In desperation he bathed daily in water to which an increasing number of oleoresin drops were added. He finally reached a "dose" of 30 ml. in 4 gal. of water. Significant dermatitis did not occur during the procedure. It is said that he became immune to leaves, though this was not substantiated conclusively.

The following brief study explored this method further.

Five-milliliter quantities of PDC acetone solution 100 times more dilute than the concentration required to produce a visible dermatitis were swabbed daily over different body regions of three subjects. Each day a new area was treated, for example, the arm, leg, abdomen, etc.; the same region was never re-treated except after an interval of a week or more. No change in sensitivity was realized after one and two months, even though mild dermatitis occasionally resulted. Thereafter, the concentration was increased 10 times, with more frequent bouts of mild dermatitis. Attempts to increase the concentration another 5 to 10 times immediately precipitated a dermatitis. After another eight weeks, there was no reduction in sensitivity. It is improbable that hyposensitization can be produced by subdermatitic exposures.

With the thought of inquiring into the possibility of local hyposensitization, patch tests with subdermatitic concentrations were repeated at the same site every three to four days for four months in three subjects. Occasionally, mild dermatitis developed. At the end, the treated site was no less sensitive than elsewhere. This finding should not be confused with the nonspecific local hyporeactivity of skin which has just recovered from an acute inflammatory dermatitis.[1] Later, healed sites tend to become hyperreactive and may remain so for 10 years.[23]

The next effort concerned the experimental demonstration of hardening. Eight moderately sensitive, rather stoical, prisoners with PDC titers ranging from 1:10,000 to 1:100,000 agreed to participate. All were leaf-sensitive. The performance of these subjects was nothing short of heroic. Despite continuous dermatitis over many months, none defected, but they went cheerfully on in the best research tradition. Each day each subject was patch-tested with a concentration just capable of producing a sharp dermatitis in a circular area about 1 in. in diameter. A new spot was selected each time. The plan was to increase the strength gradually as the subject became tolerant of each dilution.

The responses of half these subjects were somewhat puzzling in the early phase. After 15 to 25 daily patches, the trend was toward greater, not less, reactivity. Concentrations which at the start produced a mild dermatitis subsequently caused greater inflammation, although inconsistently so. Two agencies seemed operative: (1) the sensitivity was being deepened by repeated daily application of the allergen, an intensive immunologic experience to say the least, and (2) there was a nonspecific increase in the irritability of the skin, a consequence of repeated dermatitis. That this does happen with primary irritants has been demonstrated by others [42] and by us experimentally.‖ Happily we were not put off by this seemingly paradoxical development, and all the subjects began to have diminished reactions to the first concentration after two to three months of daily exposures. The concentration was then increased 10 times, precipitating a sharp dermatitis. Disconcerting fluctuations in the reactions, sometimes stronger, sometimes weaker, occurred from test to test, more so in some subjects than others. Nonetheless, as the applications continued there was an un-

‖ In a forthcoming paper, W. Epstein and I label this increased nonspecific generalized reactivity of the skin induced by repeated bouts of dermatitis "conditioned irritability of the skin."

mistakable decline in the sensitivity, though at rates vastly different for different subjects. With the jump to the next 10-times-stronger concentration after several more months, the entire sequence was reenacted, with all its variability. After more months of this assault, it was possible to apply 1% PDC without reaction, and finally 10% PDC was applied, with no more reaction than the original patch test. This took over 300 applications and 9 to 11 months. By this time there was scarcely a region on the body which had not been the site of a dermatitis! The finger-leaf test produced no reaction in any of these eight subjects. True desensitization had been achieved. Subsequently I found that Shelmire had performed a similar experiment on a young male subject.[43] At four- to seven-day intervals, 15 to 30 oleoresin patch tests were simultaneously applied for six months! At the end neither leaves nor the 1:10 dilution produced a dermatitis—in short, there was true desensitization.

Topical desensitization is more of theoretical than practical interest in Rhus prophylaxis. In industry, however, hardening has definite practical consequences; it may enable a worker to stay on his job. The state of complete resistance to a contact allergen may be brought about in a much shorter time than in the current study, where the dermatitis was limited to 1-in. circular areas. More extensive dermatitis establishes resistance quickly in persons hardy enough to stand the cutaneous punishment. There is no question that the skin must be cruelly assaulted. The interesting point is that the total quantity of allergen which produced complete clinical immunity is much less than that which given orally or by injection produces only a moderate diminution in sensitivity. Is this because the shock organ itself is a more efficient immunologic route? Are other associated factors participating, such as the necessity of producing diffuse or persistent dermatitis? Many questions arise. That the phenomenon is at least partially specific immunologically is demonstrated by the fact that two of the Rhus-desensitized subjects retained a sensitivity to dinitrochlorobenzene. Additionally, the dermatitis itself may in time induce a nonspecific adaptation or conditioned tolerance. Acquired tolerance to pharmacologic agents is well known. Without more work, further speculation is fruitless. It should be emphasized that hardening is a generalized state not at all comparable to the increased local resistance exhibited by the skin to repeatedly (and carefully) applied physical and chemical irritants, a process of nonspecific toughening.

Both Peck et al.[38] and Sulzberger [44] mention that hardening may be permanent, though it is more often temporary. Substantial evidence of permanent desensitization has not been given. Six subjects in the present study were available for quantitative patch testing 9 to 12 months later. All had regained their sensitivity. It should be recalled that there is a natural tendency toward loss of sensitivity with age [1]; this is a slow and inconstant process about which nothing is known. Spontaneous loss of sensitivity is clearly different from hardening.

The Pattern of Hyposensitization

Regardless of the route or the material, hyposensitization takes place in a characteristic and interesting manner, previously overlooked. By plotting the intensity of reaction (1 to 4) against concentration (quantitative patch testing) dosage-response curves are defined as previously described.[1] The concentrations employed were 1:100; 1:1000; 1:10,000; 1:100,000, and 1:1,000,000 PDC in acetone. The slope of these curves may vary considerably but is characteristic for a given person. Hyposensitization changes these curves in a typical way.

The first evidence of hyposensitization is a decline in the intensity of the reaction provoked by the highest of the series, i. e., the weakest concentration. It is the weakest dermatitis which is affected first. Only the terminal portion of the curve is altered.

With continued administration of increasing amounts of allergen, the dermatitis evoked by the next tenfold concentration begins to diminish; eventually the highest dilution no longer produces a dermatitis. Hyposensitization progressively sweeps proximally toward stronger concentrations. This process has a definite limit, previously referred to as the point of maximum hyposensitization. In general, the maximum effect is not greater than a hundredfold change in sensitivity. For example, an original 2+ dermatitis to 1:1,000,000 PDC may be reduced to approximately the same reaction to 1:10,000 PDC; the response to this dilution is seldom abolished altogether. In the case under discussion the dermatitis produced by the strongest concentration, 1:100, may or may not be weakened, depending on the subject. One can easily see how a significant change in sensitivity could be entirely missed if a single 1:100 patch test were used exclusively. The proportionate reduction in sensitivity takes place no faster and has no greater magnitude in the case of initially weak sensitization. For instance, if the initial titer is 2+ to 1:10,000 PDC, the subject will still react to 1:100 after maximal hyposensitization and the amount of allergen required to effect this hundredfold change will be just as great as if one were hyposensitizing an extremely sensitive subject. Whatever the original sensitivity, and within limits no matter how great the amount given, only a limited fraction of the sensitivity is abolished. This description is necessarily gross; there are decided individual variations. Some respond more readily than others; an occasional subject experiences only a minimal change in sensitivity. Inspection of the accompanying sample curves shows the general pattern at a glance (Figs. 1, 2, and 3).

In view of these serious limitations, the question of clinical applicability arises. Is hyposensitization worth while? It was shown previously that many persons who gave positive patch reactions to PDC were nonetheless clinically immune to leaves, so-called subclinical reactors. These were feeble reactors to PDC with titers of 1:100 and sometimes of 1:1000. All leaf-sensitive persons reacted to 1:10,000 PDC. For purposes of discussion, we may assume that 1:10,000 PDC reactivity defines the clinical level of sensitivity. If no more than a hundredfold decrease in sensitivity is possible by oral or intramuscular methods, one would never expect to produce clinical immunity in a subject originally sensitive to 1:1,000,000 PDC. This is precisely the case. Indeed, after maximal hyposensitization, the finger-leaf test invariably produced a sharp dermatitis. Some exquisitely sensitive per-

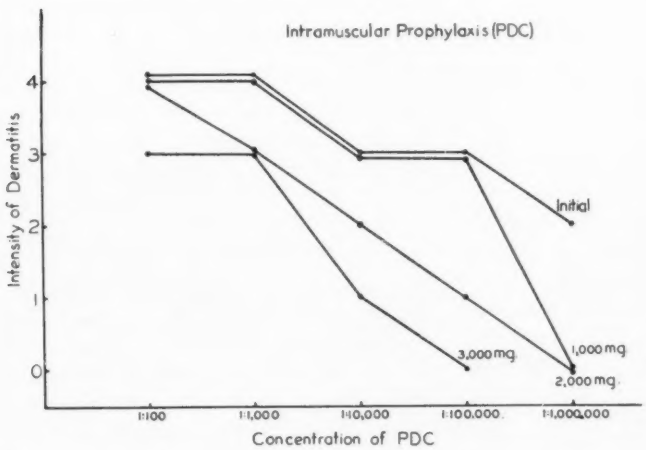

Fig. 1.—Maximal intramuscular hyposensitization of a highly sensitive subject. One thousand milligrams changed only the reaction to the weakest dilution. Even after maximal hyposensitization with 3000 mg., the stronger concentrations still produced intense dermatitis, as did bruised leaves.

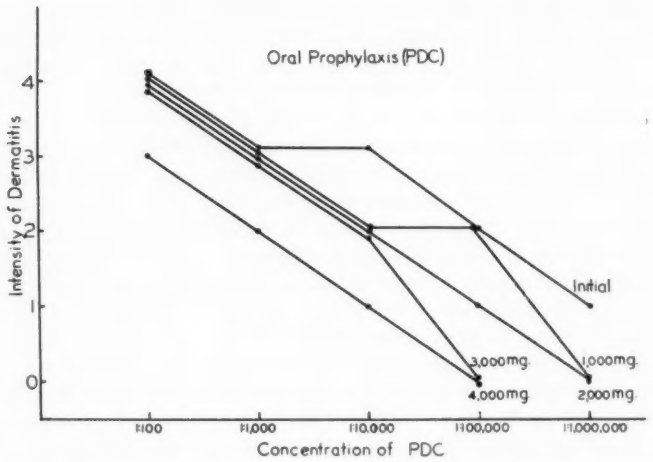

Fig. 2.—Maximal oral hyposensitization of a highly sensitive subject. The pattern is the same; chiefly the terminal portion of the curve is changed.

sons can react to 1:50,000,000 PDC, and in them the clinical immunity would be even less. On the other hand, with weak sensitivity (1:10,000 PDC titer) maximal hyposensitization may produce complete clinical resistance. Such persons by and large would not be in great need of hyposensitization. Unhappily, the best results are achieved in those who need prophylaxis the least.

Up to this point, these limited results would scarcely constitute a strong endorsement for hyposensitization. But there is another dimension not revealed by the raw data of quantitative patch testing which greatly strengthens the case, namely, reduction in the duration of the dermatitis. As a rule high sensitivity is accompanied by protraction of the acute blistering phase for 8 to 20 days; a dermatitis which oozes and itches for more than 10 days is tormenting beyond description. As a rule, the duration is directly proportional to the sensitivity as defined by titer. By contrast, the acute phase lasts a few days to a week in the mildly sensitive person, even though the dermatitis may be of maximal intensity at its peak. A heavy leaf exposure may produce an eruption in a mildly sensitive person which is just as inflammatory as that which

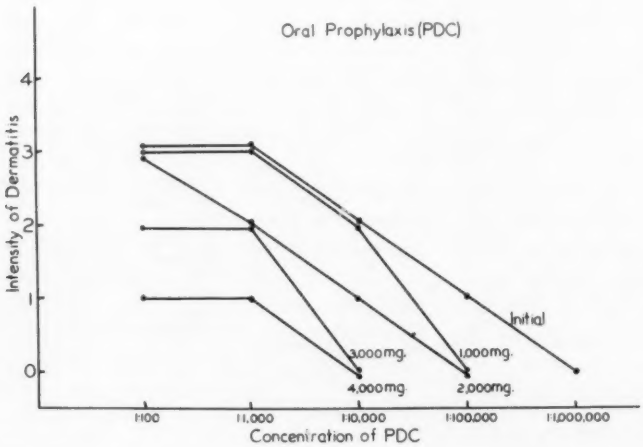

Fig. 3.—Maximal oral hyposensitization of a moderately sensitive person. Again only a limited fraction of the sensitivity was abolished. At the end, however, leaves produced only a mild reaction.

customarily occurs in the highly sensitive; the less sensitivity of the former is made known by the shorter course. This difference is an important one and requires emphasis. Thus, duration of the acute stage is an indirect measure of the degree of sensitivity. As hyposensitization proceeds, there is almost invariably a shortening of the acute phase; the dermatitis heals more quickly. Therefore, hyposensitization accomplishes more than is evident from dosage-response curves. Often the dermatitis, no matter how inflammatory, suddenly dries up in five to nine days. In consequence, the highly sensitive person may still suffer equally severe attacks but the shorter course is a decided boon. This accomplishment alone possibly justifies hyposensitization. There was one further benefit of hyposensitization. In highly sensitive persons Rhus dermatitis rarely remains confined to the site of contact. Characteristically, lesions develop in other areas, such as the face and genitals, owing to transfer of traces of allergen via the fingers or clothing. This adds considerably to the patient's woes. Generalized or widespread dermatitis almost invariably signifies high sensitivity. Extraordinarily small quantities of allergen may excite a dermatitis.[1] Because it is precisely against trace amounts that hyposensitization is most effective, spreading is less likely and the lesions are milder.

The advantages of hyposensitization are threefold; in the order of probability they are (1) shorter duration, (2) less spread, and (3) milder dermatitis. Often only the first two are realized in significant but variable degree. The protection is partial and relative, depending, of course, on the degree of exposure.

Duration of Hyposensitization

Repeated quantitative patch tests and finger-leaf tests on institutionalized subjects up to periods of 18 months furnished an opportunity to determine the duration of hyposensitization. Not only were previous estimates, ranging from months to years, usually pure guesses, but hyposensitization was often fictitious in the first place. Material data are given by Gold and Masucci,[45] who found a considerable return of sensitivity by six months. In the present study, maximal hyposensitization endured for about four to six weeks after oral prophylaxis and about eight to ten weeks after intramuscular treatment. The more prolonged effect of the latter is probably due to persistence of the allergen at the injection site. Thereafter the hyposensitization began to wane gradually; restoration of the original sensitivity required six to eight months. There was a disconcerting amount of individual variation; the crudities of patch testing did not make for confidence in establishing the precise end-point of this recovery process. The pattern of the dosage-response curves during recovery was the exact reverse of hyposensitization. First the dermatitis to the stronger concentrations increased, and subsequently reactions began to occur at higher dilutions.

One may conclude that hyposensitization is a temporary state. Its effects begin to wear off quickly even though the period required for restoration to the original state of patch-test sensitivity may exceed half a year. During recovery the amount of clinical protection declines progressively. Observations on hardening in industry lead to the same conclusions. If through absence the worker has no contact for weeks or months, he will again break out upon resuming his job. Continuous exposure is a prerequisite for maintaining the hyposensitization.

The practical implications are obvious; hyposensitization must be repeated each season, or a maintenance dose has to be given perennially. Maximal hyposensitization should be established before the leaves come out in spring, the most hazardous period for the poison-ivy-sensitive. A daily maintenance dose is probably advisable during the early months of the summer. If occupational or recreational habits make

continuous exposure inevitable, a maintenance dose is clearly indicated.

A number of hyposensitized volunteers who received no further allergen after June were followed the next season. When they started over again in February or March, there was often unmistakable evidence of some lingering hyposensitization, although patch-test reactivity had been restored to its original status. Fewer allergic side-reactions were encountered, and this enabled more rapid advancement of the doses. In short, there was often enough protection left to reduce intolerance. Doses which produced a rash during the first hyposensitizing course often failed to do so during the second. In this respect, too, hyposensitization produced effects not completely revealed by quantitative patch testing. Even though quantitative patch testing does not tell the whole immunologic story, it is still the most reliable criterion for assessing changes in sensitivity objectively. From the practical standpoint, the case for hyposensitization is somewhat brighter than is indicated by the raw data of quantitative patch testing.

Maintenance Dosage

The subject of maintenance dosage was incompletely studied. Present knowledge is tentative.

With intramuscular PDC prophylaxis, maximal hyposensitization was maintained by the injection of 100 mg. (1 ml. of 10% solution) every six to eight weeks. Lower quantities or longer intervals were inadequate. Two hundred milligrams (2 ml. of 10% solution) every 10 to 12 weeks is effective but produces too much local soreness and stiffness. These data were derived from about 100 subjects.

Five drops of a 10% alcoholic solution of PDC (approximately 15 mg.) daily by mouth was an adequate maintenance dose in 20 subjects. Lower amounts were not investigated.

Toxicology of Rhus Antigens

Because these allergens are phenols, and hyposensitization requires large amounts, the question of primary toxicity is important. Some aspects have been previously discussed.[1] We are concerned here with primary toxic effects, not allergic toxicity. Obviously this can be evaluated only in nonsensitive subjects, although little has been done in this regard. Howell et al.[46] have reviewed the scanty literature, although most of the information that they cite relates to sensitive subjects. With both lethal and sublethal doses of concentrated oleoresin these workers could not produce kidney damage in nonallergic rabbits. Shelmire, who is not sensitive, ingested 2.0 ml. of a 10% solution of oleoresin without ill effects.[47]

The current studies were as follows.

Eleven healthy nonsensitive adult prisoners received 1 ml. of 10% PDC in sesame oil intramuscularly once a week for 40 injections (4000 mg. total). There were no adverse clinical effects, save local tenderness. The following laboratory examinations did not deviate significantly from the pretreatment values: hemoglobin, red blood count, blood urea nitrogen, fasting blood sugar, cephalin flocculation, serum bilirubin, phenolsulfonphthalein excretion, urinalysis. Six persons showed a leukocytosis up to count of 16,000, of whom five had eosinophilia of between 5% and 12%. Sesame oil itself may produce this degree of eosinophilia when 1 ml. is injected weekly. Löffler et al.[48] noted that certain vegetable oils had this property.

Another six nonsensitive subjects ingested 100 mg. of PDC (1 ml. of 10% alcoholic solution) daily for 40 days (4000 mg. total). The routine blood and urine tests remained normal.

Five nonsensitive subjects ingested 100 mg. of the oleoresin (1 ml. of 10% alcoholic solution) daily for 30 days (3000 mg. total). No ill effects were observed.

At these dosages the toxic effects of Rhus allergens in nonsensitive persons are apparently negligible.

Toxic Effects in Sensitive Subjects

The undesirable side-effects accompanying hyposensitization are attributable, so far as present understanding goes, entirely to allergic reactions. Shelmire has given a good account of those following oral prophylaxis.[47,49] The main signs and symptoms are mucocutaneous: pruritus ani, flares of healed sites, rashes, dyshidrosis, and urticaria. The literature is strangely silent about reactions following intramuscular prophylaxis, probably because of impotence of the extracts and the tiny doses. The kinds of manifestations possible when Rhus allergens enter the sensitized body by various routes have been discussed previously.[1] Though the skin is the principal shock organ, allergic contact dermatitis is in reality a generalized allergic state wherein many tissues are potentially reactive. The permeation of the entire body by abnormally high concentrations of allergen during hyposensitization creates an artificial opportunity to witness a variety of unusual allergic expressions.

At the outset it should be appreciated that hyposensitization involves the administration of substances which are specifically noxious for the recipient. The incidence and gravity of unwanted side-effects are directly proportional to the degree of sensitivity and the amount of allergen. With high sensitivity even a little allergen may be hazardous; with low sensitivity reactions occur only with high doses. Practically speaking, the probability of adverse effects is a matter of dosage. Some examples are as follows: A single 200 mg. dose of PDC orally regularly produces rashes in subjects of low sensitivity, but 50 mg. does not. By contrast, 25 to 50 mg. of PDC orally in highly sensitive subjects invariably produces cutaneous reactions; even 1 to 5 mg. is harmful for some.

Figures on the incidence and varieties of side-reactions have meaning only in relation to the known variables which determine them, namely, the amount of antigen introduced within a given time, the original level of sensitivity, and the route of administration.

In my own trial and error searches for a practical program of prophylaxis I have tried many different schemes, not without misadventures. When it became evident that hyposensitization required a large total dose, efforts were made to give the largest possible quantity in the shortest possible time. The frequency of side-reactions exceeded 90% in the first few groups in whom "massive" hyposensitization was tried. This was a period of alternating optimism and despair, with suffering equally divided between the subjects and the investigator. Bit by bit it was necessary to retrench, making the schedules more and more conservative, starting with lower doses, and increasing more slowly. The total time required lengthened proportionately. The condensate of this experience with over 1500 subjects of all degrees of sensitivity, treated with PDC under different schedules, will now be given in synoptic form. My experience with oleoresin is too meager to present.

Cutaneous Reactions

The dermatologic side-reactions included pruritus, erythematous rashes, flares of healed sites, urticaria, dyshidrosis, erythema multiforme, and pruritus ani. Pruritus, generalized or localized, headed the list in frequency. Often this occurred in healed sites (subjective flares). It was either diffuse or curiously localized to some particular region, such as the feet, arms, etc. Next came erythematomacular or erythematopapular "toxic" rashes, often resembling drug eruptions. These were sometimes generalized or localized in single or multiple patches. An eruption localized to old traumatic scars occurred in two cases. My experience is similar to Shelmire's[47] in that vesicular reactions resembling the charac-

teristic picture of contact dermatitis were never encountered. (A pitfall here is the possibility of true Rhus contact dermatitis while the subject is being hyposensitized.) Dose for dose, cutaneous rashes were far more frequent with oral than with intramuscular administration, probably reflecting higher blood levels from more rapid absorption. This difference was narrowed by dividing the daily oral dose into two portions separated by 12 hours. As a crude estimate, about one-half of the patients of moderate to severe clinical sensitivity, subjected to conservative oral prophylaxis (beginning with about 3 mg. and increasing gradually to a maximum of 100 mg. daily), will experience either pruritus or a rash at some time. With conservative intramuscular prophylaxis (beginning with 1 mg. and increasing to a weekly maximum of 100 mg.) rashes other than local ones at the injection site occur in about 10%. More detailed information about conservative prophylaxis will be given later.

Flares of healed sites occurred most irregularly and unpredictably. With conservative oral or intramuscular prophylaxis, flares of healed sites did not exceed 10%. Even with large initial doses they were uncommon. Nor did they necessarily occur in the most recent sites of dermatitis. Sometimes, a six-month-old patch-test site flared, while more recent ones, even those a week old, did not. In fact, it was impossible to predict which, if any, of many healed sites of different ages, two weeks to eight months, would flare. The inconstancy of the phenomenon was striking. This seems to correspond to the finding that flares of existing lesions do not occur regularly when the allergen is given during the acute dermatitis.[1] By contrast, in allergic contact dermatitis due to Krameria, Grolnick [50] produced flares rather regularly in a definite sequence which began with the most recently healed site; each site flared in the order of its respective age, the oldest site flaring last. My experience is completely different. Why flares occur in some sites and not others is a mystery. The longest interval for a flare was 18 months. Flares have been known to occur after years. On the other hand, pruritus of healed sites without objective exacerbation was a more frequent phenomenon (subjective flare).

Urticarial reactions were strongly dependent upon dosage. Hives were most frequent and persistent with intramuscular prophylaxis (contrast rashes). High sensitivity is a prerequisite for their appearance. The previous paper should be consulted for a theoretical discussion of hives as an associated manifestation in allergic contact dermatitis.[1] When a single 100 mg. dose of PDC is given intramuscularly to highly sensitive subjects, more than 75% will develop hives; these may persist for several weeks. Angioedema of the face occurred twice with these dosages. The onset is rarely before 24 hours and may be delayed 12 days. A single 50 to 100 mg. dose of PDC orally produces hives in less than 25% of the highly sensitive; these are transient, disappearing within 12 to 48 hours. With conservative oral prophylaxis, urticaria was infrequent, not exceeding 5%. Nothing resembling anaphylaxis was encountered.

Dyshidrosis of the palms was a rarity, with less than 1% occurrence with conservative prophylaxis. High doses, especially intramuscularly, provoked this expression more frequently.

Rarest of all cutaneous manifestations was bullous erythema multiforme. This never occurred with conservative prophylaxis or with any oral dose. It was seen twice with massive intramuscular prophylaxis using 50 to 100 mg. weekly from the very start.

Pruritus ani is a maddening complication of oral hyposensitization. With conservative prophylaxis beginning with a single drop of 10% PDC in sesame oil the incidence was about 10% in the highly sensitive. It could not be prevented by reducing the starting dose to 1 drop of 0.5% solution. Various means of eliminating this

troublesome symptom were tried. This effort was finally successful by the simple device of dissolving 10% PDC in ethyl alcohol along with 2.5% of the wetting agent Aerosol OT‖ [bis(2-ethylhexyl)sodium sulfosuccinate]. A milky emulsion results when drops are added to a glass of stirred water. Absorption is evidently complete from this vehicle. With conservative prophylaxis using this preparation and with division of the daily dose into two portions, pruritus ani was encountered only once in over 150 cases.

Some special comments are required for the local reactions following intramuscular injections of 10% PDC in sesame oil. These usually occurred only in very sensitive subjects. The onset was variable, 2 to 12 days. With single doses of 50 to 100 mg., more than three-quarters of highly sensitive subjects had adverse local reactions. With conservative prophylaxis, the incidence was still about 20% during the first three injections but the severity was less. Among persons of equally high sensitivity, it was impossible to predict the intolerant. The mildest reaction was a localized, tender, slightly inflammatory, subcutaneous nodule. Deep indurated plaques sometimes developed. The severest expression was a massive angry cellulitis, with extensive swelling, pain, tenderness, and fiery redness. This had a gravitational pattern. With deltoid injections, the red swelling extended gradually downward, sometimes to the finger tips. With lateral thigh injections, it descended to the toes. The joints, or at least the periarticular tissues in the path of this spreading cellulitis, occasionally became markedly swollen. An acute dermatitis sometimes surmounted the cellulitis. The aspect was most distressing. Muscle pain, soreness, and tenderness were often highly disagreeable. These latter symptoms could occur without any visible skin change. Rarely a sterile abscess formed which usually drained spontaneously. Subcutaneous injections invariably produced sterile abscesses in highly sensitive subjects. These deep muscle and subcutaneous reactions are evidences that the shock organ in allergic contact dermatitis is not exclusively the upper skin. They do not occur in the nonsensitive.

‖ American Cyanamid Company, New York.

Mucous Membrane Reactions

It is only in the highly sensitive that the oral mucous membranes will react to contact allergens, and then the local concentration usually has to be fairly high. Ten drops of 10% PDC solution will always produce an inflammatory stomatitis when placed upon the tongue of a highly sensitive person. All the mucous membranes of the mouth may be affected. With conservative oral prophylaxis stomatitis occurred in about 20% when 10% PDC in sesame oil was dropped on the tongue and then a glass of water was given. The use of the ethyl alcohol-Aerosol OT vehicle greatly reduced the incidence of stomatitis; however, one has to be sure that the drops are put into a full glass of water. With conservative prophylaxis using this vehicle, stomatitis, usually mild, developed in about 5% of the subjects.

Systemic Reactions

Systemic reactions were never encountered with conservative oral prophylaxis and will not be further discussed. Intramuscular injection of 10% PDC, especially in larger initial doses, produced a variety of systemic adverse reactions in highly sensitive subjects. These were mild and infrequent with conservative prophylaxis but severe and frightening with more vigorous treatment. With starting weekly injections of 25 to 50 mg. increasing rapidly to 100 mg., constitutional reactions were seen in about 15%. These included temperature up to 103 F, grippe-like syndromes, muscle aches, asthenia, meningismus, bouts of coughing or wheezing, and headaches. The same patients invariably had severe local reactions. With 200 mg. injections, constitutional reactions were severer and more frequent. No anaphylactoid reactions occurred. Seven

cases of Löffler's syndrome were encountered with high initial weekly doses (100 mg.). This complication, and a hypothesis concerning its pathogenesis, has been previously reported.[51] It should be emphasized that the severer complications occurred only with larger doses in highly sensitive persons. Even after maximal hyposensitization, 2 ml. of 20% PDC intramuscularly (200 mg.) still provoked constitutional and local reactions, affirming again that complete desensitization of highly sensitized persons is impossible.

Among the uncommoner reactions in intolerant patients was generalized adenopathy, and in one case there was herpes zoster.

Hematologic Reactions

The cell which most sensitively reflects the impact of orally or parenterally administered Rhus antigens in sensitized persons is the eosinophil. Eosinophilia is an inevitable development in every instance of clinical sensitization, whether mild or strong, given large quantities of allergen, especially intramuscularly. Single 100 mg. intramuscular doses in highly sensitive subjects produced eosinophilia ranging from 59% to 20%. Even after hyposensitization is well under way, weekly 100 mg. injections often induce eosinophilia of between 10% to 30%. With weekly 2 ml. injections of 10% PDC (200 mg.) the eosinophilia commonly exceeds 30% and may reach 55%. When weekly 100 mg. doses are continued to a total of 3 or 4 gm. the eosinophilia persists in the highly sensitive. As maximal hyposensitization is approached the eosinophilia may decline, especially in the moderately sensitive. As a matter of fact, the degree of eosinophilia following standard intramuscular doses is a fairly accurate hematologic index of the degree of sensitivity. Eosinophilia is invariably present in persons with marked side-reactions. Even with conservative intramuscular prophylaxis, eosinophilia of some degree is frequent, though of less magnitude, in the highly sensitive. It should be remembered that weekly 1 ml. injections of sesame oil alone can produce mild degrees of eosinophilia. With conservative oral prophylaxis, eosinophilia is less intense and often absent. Mild eosinophilia, present in the early stages, characteristically disappears later. Eosinophilia may be considered a primary allergic response of the hematopoietic system. Eosinophils often congregate in lesions of acute allergic contact dermatitis.

Leukocytosis, ranging from 10,000 to 24,000 often, but not always, accompanies intense eosinophilia and is in proportion to it. As hyposensitization proceeds, the leukocytosis tends to diminish or disappear, although the eosinophilia may persist. Leukocytosis is a typical accompaniment of severe intolerance reactions. It does not precisely parallel sensitivity, as does eosinophilia, but is rather a reflection of the total adverse impact of a high quantity of allergen on the intolerant host. Unlike eosinophilia, leukocytosis is not a primary allergic reaction.

With conservative oral or intramuscular PDC prophylaxis other changes in the peripheral blood were uncommon. Occasionally, a mild anemia followed in the wake of systemic reactions or when leukocytosis and eosinophilia were marked. Bone marrows were not examined.

Other Toxicologic Studies in Hyposensitized Subjects

With conservative oral or intramuscular prophylaxis no significant changes were revealed in the following tests: urinalysis, blood urea nitrogen, cephalin flocculation, serum bilirubin, total protein and albumin-globulin ratio, fasting blood sugar, and phenolsulfonphthalein excretion.

With massive intramuscular prophylaxis an elevated BUN was found twice (the values were 46 and 68 mg., respectively). Transient mild abuminuria accompanied intense intramuscular prophylaxis in a few cases with marked hematologic abnormalities. Signs of kidney damage were thus

uncommon. To date there is little evidence that the kidney is an allergic shock organ.

Widespread Rhus dermatitis may impair kidney function, as discussed in a previous paper, but serious disorders such as glomerulonephritis cannot properly be attributed to the administration of Rhus allergens.[1]

Shelmire [23] gave a patient the huge total dose of 8.5 oz. of 4% oleoresin over a two-month period, the largest on record for this material, and found no urine or blood abnormalities or other signs of harm.

Hyporeactivity

A rather regular finding was a temporary state of lowered reactivity following severe cutaneous effects induced by a large dose of allergen. Not only was this evident in patch tests, but after recovery the subjects could often take the same dose with impunity. This same refractoriness sometimes follows severe Rhus dermatitis.[1] It is not known for certain whether this is specific immunologic hyposensitization, a nonspecific hyporeactivity, or both. It does not occur after mild allergic reactions. The dose or exposure must be a "shocking" one. Shelmire [23] gives a striking illustration. He administered a "shock" dose (60 drops of 4% oleoresin daily for five days) to a highly sensitive nurse at the very time when she was suffering from the effects of a prior dose which produced a widespread rash, pruritus ani, and dyshidrosis. A generalized fiery red eruption developed, with great edema of the extremities. Pruritus ani et vulvae completed the picture of misery. After this, bruised leaves produced no reaction whatsoever; in short, there was complete desensitization. Whether this is a special instance of hardening cannot be answered at present.

Effect of Corticosteroids

Corticosteroids were a blessing in this study. Without them, exploration of various dosages, especially the bolder ones, could not have been attempted. Corticosteroids rather promptly controlled adverse side-reactions of all kinds; thus, painful circumstances were aborted.

It was found, as reported elsewhere,[52] that combining hydrocortisone with 10% PDC in sesame oil enabled conservative intramuscular prophylaxis to proceed more or less routinely in those susceptible to adverse local reactions. Twenty-five milligrams of hydrocortisone in the same syringe with each weekly dose in the early phase of hyposensitization largely suppressed local reactions. There was no interference with hyposensitization. With massive intramuscular prophylaxis, 100 mg. of cortisone or its equivalent daily by mouth was often ineffectual or only partly helpful. Hives, in particular, were especially difficult to control. This quantity by mouth was highly satisfactory in controlling local and other adverse reactions with conservative intramuscular prophylaxis.

With conservative oral prophylaxis, skin rashes and pruritus are the complaints which most frequently prevent advancing the doses in the prescribed manner. Some patients get "stuck" even with 1 or 2 drops of the 10% alcoholic solution of PDC. This barrier can generally be overcome by the daily administration of 50 to 100 mg. of cortisone acetate or its equivalent daily (10-20 mg. prednisolone), depending on the severity of the reaction. Forty to eighty units of repository corticotropin injection (Corticotropin Gel) twice weekly has the same suppressive effect. Some patients will "break through" despite corticosteroids as the daily dose increases. Corticosteroids certainly cannot nullify large doses of allergen. Even with corticosteroids the dosage must be cautious and individually regulated. It is useful to help the patient over the early stage when intolerance appears with 5 drops or less. After a dosage of 5 to 10 drops is reached, the subject can often proceed in the routine manner, without the covering effect of corticosteroids. This increased resistance to small doses which were formerly troublesome is evidence of developing hyposensitization. It becomes manifest long

before there is a change in the quantitative patch tests. Again, patch tests do not completely portray the subtleties of hyposensitization.

It was desired to know whether cortisone interfered with hyposensitization. Six highly sensitive experimental subjects were given 100 mg. of cortisone acetate daily for 10 weeks while they were being hyposensitized. The doses were rapidly increased, until a daily total of 30 drops of 10% PDC in alcohol was reached. The total quantity was 3000 mg. One week after cortisone was stopped, quantitative patch testing revealed that hyposensitization had occurred in the usual fashion. In reasonable quantities corticosteroids seem to have little influence on the hyposensitization process; likewise they do not prevent sensitization.

Fate of Rhus Allergens Within the Body

Until analytic chemical methods are applied to the problem of the distribution and excretion of Rhus allergens, knowledge must be small. Some preliminary information has been gained by the exceedingly crude technique of biological patch testing.

In the natural state, Rhus allergens are, of course, water-insoluble; none pass into water extracts. Shelmire [47] ingested 2 ml. of 10% oleoresin, collecting his urine and feces for three consecutive days. He claims, with questionable proof, that 30% was excreted in the urine and 70% in the feces. With an equal quantity injected intramuscularly he obtained the same results. He further found that unconcentrated urine and the blood could give positive patch-test reactions if large amounts of oleoresin were ingested. The allergen is obviously solubilized after absorption and will appear in urine dialysates.

I have been unable by patch testing to detect the allergen in blood or urine of four nonsensitive subjects who received intramuscular injections once with 400 mg. of PDC. Evidently release is too slow. These same subjects next received the same dose by mouth. The 24-hour urine collections concentrated to approximately 20 ml. by evaporation produced positive patch tests in highly sensitive subjects. The sera of two of the four contained traces of allergen four hours after ingestion, producing a weakly positive patch test. Obviously the concentration of allergen in the blood is higher after oral ingestion, but these levels are of short duration. The greater incidence of skin rashes with oral administration testifies to this fact. These are common with doses which would give no trouble intramuscularly.

Mechanism of Hyposensitization

Knowledge of the sensitization process and the "antibodies" engendered is mostly hypothetical. It is hardly likely that "desensitization" will be understood before sensitization itself. The question of what happens during hyposensitization is an important one. Unfortunately most of the following studies show what does not happen.

First of all, hyposensitization is a specific immunologic process directed toward the homologous allergen and not others. Four subjects who were deliberately sensitized to either monobenzylether of hydroquinone, *p*-nitrosodimethylaniline, or dinitrochlorobenzene, did not, after Rhus hyposensitization, react any less strongly to these unrelated allergens by quantitative patch tests.

The serum electrophoretic pattern in two maximally hyposensitized subjects remained unchanged.

It was impossible in a score of experiments to demonstrate any circulating blocking substance in the blood of hyposensitized subjects. Hyposensitized whole blood and serum was injected intracutaneously into moderately sensitive subjects at varying times before the sites of injection were patch tested. There was no inhibition. Incubation of varying concentrations of pentadecylcatechol with hyposensitized sera did not alter the dermatitis produced by patch testing with these sera.

The recent demonstration of passive transfer of Rhus sensitivity in humans by Epstein and me [53] made it possible to look a little deeper. Leukocytes from three hyposensitized donors readily transferred PDC sensitivity to three originally nonsensitive subjects. The recipients, but not the donors, reacted to 1:100 PDC. Evidently, hyposensitization does not suppress the synthesis of "antibodies" and their hematogenous distribution to the tissues via lymphocytes. The skin-sensitizing substances, whatever they may be, continue to be produced during hyposensitization, probably in normal amounts. The fact that hyposensitization begins to wane so quickly after treatment is stopped indicates the same thing. Two mildly sensitive subjects who had been hyposensitized to the point where they no longer reacted to 1:100 PDC did react to this concentration after receiving leukocytes from highly sensitive donors. In other words, the hyposensitization was overcome by the passive acquisition of fresh "antibodies." It may be inferred from this that hyposensitization is something more than simply raising the threshold of reaction of the skin by flooding it with a potentially harmful substance. If the tolerance of the skin had been raised in this way, hyposensitization could not be overcome by an injection of leukocytes.

For the moment, speculation about the mechanism of hyposensitization has no foundation. The plain truth is that we know nothing about it. Presumably the allergen in some way combines with and binds antibody so that it is no longer available for reacting with allergen.

Hyposensitization with Other Contact Allergens

Turning elsewhere for evidence of hyposensitization against other contact allergens, one generally meets the same uncertainties and controversies. Again clinical testimonies, usually uncontrolled, are found, but firm proof is hard to uncover. For example, contact sensitization to antibiotics such as penicillin and streptomycin is occasionally a problem in nurses. Successful parenteral and oral desensitization has been claimed.[54-56] Morris-Owen [57] believes that small subcutaneous injections of 1 to 20 units of penicillin daily protect subjects against contact allergens to which they are sensitive for 8 to 24 hours. Thus, they can be "covered" with these small daily injections until hardening develops naturally. "Covering" effects could not be realized in my studies.

Many different weed plants may cause dermatitis. Of these, sensitization to airborne ragweed pollens is second in importance only to poison ivy. Though this is uncommon, afflicted persons are seriously inconvenienced. Techniques for hyposensitization are based upon those used in Rhus sensitivity. It is noteworthy that the work in this area has been of an unusually sober and careful kind, free of the sensational incredible claims which have often discolored Rhus research. Without millions of sufferers clamoring for help, investigators seem to have had less trouble keeping a cool head. Using merely clinical criteria, Brunsting and Williams [58] did not obtain any benefit in 10 to 24 patients who received numerous injections of ragweed oleoresin. Ingraham [59] repeatedly injected as high as 10% concentrations of oleoresin in oil and succeeded in reducing the patch-test reactions as well as achieving marked clinical improvement of the dermatitis produced by several kinds of plants. One may be skeptical of his claim of persistence of the hyposensitization for as long as two to three years. Slater and Norris [60] state that a total of 2 ml. of the oleoresin is required orally, given over a two- to eight-month period. This roughly accords with the requirement for Rhus prophylaxis. Sheldon and Blumenthal [61] obtained good results with prolonged oral prophylaxis in 12 to 16 ragweed-sensitive patients, several of whom were shown to have experienced a reduction in sensitivity by quantitative patch tests. It

seems rather likely that with intense oral prophylaxis one can accomplish as much (but no more) in ragweed and other types of plant sensitivity as in Rhus dermatitis. Fisher [62] claims to have completely desensitized one patient.

Practical Considerations

Hyposensitization is not easily achieved in allergic contact dermatitis. One is confronted with the thorny problem of giving a large amount safely. The following synopsis might serve as a guide for developing a practical method of Rhus prophylaxis.

Intramuscular prophylaxis is altogether impractical. Too many injections are required, and, even with conservative dosage schedules, adverse reactions are too numerous and too severe. For the record, the program referred to in this paper as conservative prophylaxis is as follows. Ten per cent PDC in sesame oil with two per cent aluminum monostearate was used. To prevent oxidative blackening 0.1% of the antioxidant Tenox¶ was incorporated; however, the potency of the allergen is not appreciably affected by this discoloration, even if the originally yellowish mixture turns deep black through exposure to the air. The injections are given intramuscularly at weekly intervals as follows:

Injections	Volume, ml.	PDC, mg.
1	0.03	3
2	0.6	6
3	0.10	10
4	0.20	20
5	0.40	40
6	0.60	60
7	0.80	80
8	1.00	100

Weekly 1.00 ml. injections are continued to a total of 2500 grn. for cases of average sensitivity (total 2.5 ml.). This will require approximately six months if intolerance does not compel slower progress. In the event of local reactions, 25 mg. of hydrocortisone acetate may be incorporated in the first six to eight injections. Hyposensitization can be maintained by a 1 ml. injection every six to eight weeks.

¶ Eastman Chemical Products, Inc., division of Eastman Kodak Company, Kingsport, Tenn.

Oral prophylaxis is the preferred route. The doses can be advanced slowly by small increments. Signs of intolerance can be recognized early and can be intercepted. The patient controls the entire procedure. PDC is theoretically advantageous because of its purity and stability. Unfortunately, its synthesis is somewhat costly, and it will not be available in the immediate future. The conservative program of prophylaxis is as follows. Ten per cent PDC in ethyl alcohol with two and five-tenths per cent Aerosol OT and one-tenth per cent Tenox is dispensed in a dropper bottle (30 drops equal approximately 1 ml.). The required number of drops is added to a full glass of water. The emulsion is stirred with a glass or disposable straw and is drunk through the straw. The dosage schedule is as follows.

First week	1 drop daily
Second week	2 drops daily
Third week	3 drops daily for four days and increase by 1 drop every four days to a daily total of 30 drops

After the first week the daily dose is divided into a morning and an evening portion. This reduces intolerance by lowering peak blood levels. For convenience, after reaching the 30-drop maximum for a week without mishap patients may take this amount in a single dose. For the average case of sensitivity this dosage is continued until 35 ml. have been ingested. A single 5-drop dose daily, possibly less, will maintain the hyposensitization. Through experimentation, adventurous subjects may, after the first two weeks, advance the doses more rapidly, every two to three, instead of four, days.

If intolerance is encountered with less than 5 drops, time may be saved by "covering" the patient with 50 to 100 mg. of cortisone taken orally or its equivalent daily (15 to 20 mg. of prednisolone). Some patients are intolerant of 1 drop. With cortisone the dosage from the start may

generally be increased by 1 drop every three days to a total of 10 drops daily (5 drops b. i. d.). Then cortisone is stopped; the patient goes back to 5 drops and advances thereafter in the usual fashion. The necessity for individual management is emphasized. Even 100 mg. of cortisone will not allow as much as 5 to 10 drops to be taken daily without pruritus or a rash in some patients. Intolerance is most apt to occur in the early stages. This is the troublesome period. Even if the patient is forced to go slowly, every drop ingested takes him further along the road to hyposensitization. With the above schedule perhaps as many as 50% of the highly sensitive will experience some degree of intolerance somewhere along the course. They need only stop for a few days until the signs abate and resume again 1 drop lower than the last dose. Progress after signs of intolerance is a variable matter and may require that the subject advance only 1 drop weekly. The subject's outlook and enthusiasm are important. Some can face pruritus and mild rashes stoically and keep right on increasing the doses, unless severe signs ensue. Whatever the rate of increment, gradually doses will be tolerated which formerly would have produced severe intolerance. Indeed, the severer the reaction, the likelier, owing to temporary refractoriness, that the patient can tolerate considerably larger doses than those which precipitated the reaction. Severely intolerant subjects may never reach the 30-drop daily maximum. They take whatever they can until the required total is reached. A few patients have trouble exceeding 5 to 10 drops. This, of course, lengthens the procedure. The final state of hyposensitization in such patients is often below average. Conservative prophylaxis requires three and one-half to eight months, depending on intolerance and the daring of the subject.

My limited experience with oleoresin suggests that a similar schedule may be followed with use of 10% solution of ethyl alcohol, with 2.5% Aerosol OT and 0.1% Tenox. A total of 25 ml. (2500 mg. oleoresin) will give reasonable protection in the average case. The greater potency of 10% oleoresin solution shows itself in an increased frequency of stomatitis and rashes in the early stage. Perhaps less concentrated solutions should be used. Shelmire's method is a little more complicated, since three solutions of different strengths are utilized and the oil drops have first to be put in capsules. The theoretical disadvantages of the oleoresin are variable potency and some tendency toward degradation. With tested potent oleoresins, the results are certainly just as satisfactory as with PDC, and less is required. The nature of the allergen, whether synthetic or natural, pure or impure, is not consequential so far as final results or inherent difficulties are concerned. The maximal hyposensitization attained is the same in any case. Indeed, it may be stated categorically that any substance, whatever its origin, which is capable of causing a dermatitis in Rhus-sensitive persons may be utilized for Rhus hyposensitization. This is specifically true for cashew nut shell oil, which contains immunologically related allergens and will be the subject of another report. Contrariwise, it is improbable that chemically related, nondermatitogenic substances would have the biological requisites for hyposensitization. Indeed, the dermatitis-producing power is a direct measure of hyposensitizing efficiency. Hyposensitization with Rhus antigens confers resistance equally against Rhus radicans (poison ivy) and Rhus toxicodendron (poison oak).

In clinical practice, quantitative patch testing is out of the question. In consequence, there will be no good means of deciding how sensitive the subject is or how much protection he has achieved by treatment. The patient can persuade himself of benefit where none exists. Or, being still capable of acquiring a sharp dermatitis, he may underestimate a genuine change in sensitivity. Only after years of extensive experience can a reasonably accurate ver-

dict of the benefits of prophylaxis be reached by the medical fraternity.

Clues of high initial sensitivity are (1) bullous rather than vesicular eruptions, (2) dissemination to nonexposed areas, and, perhaps most important, (3) duration of the acute phase beyond 7 to 10 days.

Hyposensitization is not a trivial procedure. It should be undertaken only when the need of protection is great and exposure, unavoidable. Justification exists for the highly sensitive in whom one attack yearly may be incapacitating or for the less sensitive who experience periodic recurrences, sometimes perennially.

Summary

A definite but limited reduction in Rhus sensitivity may be attained by oral or intramuscular administration of Rhus allergens.

With oleoresin, maximum hyposensitization is obtained with approximately 2000 to 2500 mg. intramuscularly and 2500 to 3000 mg. orally. With the pure, but less potent, pentadecylcatechol, this state is reached with approximately 2500 to 3000 mg. intramuscularly and 3500 to 4000 mg. orally.

Hyposensitization occurs in a definite pattern revealed by quantitative patch tests. The reaction to the highest dilution declines first. Only the terminal portion of the dosage-response curve is notably affected. More than a hundredfold decrease in titer is rare. A given fraction of the original sensitivity may be abolished but no more, regardless of how high the total dose or the initial degree of sensitivity.

By repeatedly assaulting the skin with dermatitis-producing patch tests over a period of many months, complete clinical desensitization to leaves can be achieved. The actuality of "hardening" has been proved. Complete desensitization of the highly sensitive subject by oral or intramuscular administration is impossible.

A variety of systemic and mucocutaneous side-reactions may develop in the course of hyposensitization, accompanied by characteristic changes in the blood. The severity and frequency of these are proportional to the dosage and the sensitivity.

The legitimate objectives of hyposensitization are in order of probability (1) briefer duration, (2) less dissemination, and (3) milder attacks.

Hyposensitization is temporary. It begins to wane after a few weeks. The original sensitivity is gradually regained within 6 to 10 months, occasionally longer.

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Necrobiosis Lipoidica Diabeticorum

A Biochemical, Histochemical, and Electrophoretic Study

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Fig. 1 (Patient 1).—Necrobiosis lipoidica diabeticorum present 15 years.

Necrobiosis lipoidica diabeticorum is a chronic cutaneous disorder, occurring usually in females and found almost entirely on the anterior surface of the lower extremities. The lesions are characterized by single to multiple sharply demarcated, oval, firm, yellowish, shiny plaques with a violaceous border (Figs. 1 and 2).

The purpose of this paper is not to review the literature on necrobiosis lipoidica diabeticorum, as this has been done in the past by Hildebrand, Montgomery, and Rynearson [1] and more recently by Hare,[2] but rather to attempt to resolve the still unanswered question of its relationship to diabetes mellitus. Studies were done to determine the formative mechanism of the vascular lesions, to show possible reasons for the common occurrence of the lesion at the anterior tibial region, and to determine the reason for its predominance in females. To accomplish these objectives, a study was made of the lipid and carbohydrate metabolism, blood flow, and urinary steroid excretion. The abnormal cutaneous histopathology was reviewed by special staining methods.

Materials and Methods

Eight patients, one man and seven women, ranging in age from 29 to 49 years were studied. These patients had no previous knowledge of having diabetes mellitus, and their family histories revealed no evidence of the presence of this disease. Duration of the lesions varied from 9 months to 27 years, with the average being 17.7 years. The average age of the patients at the onset of the lesions was 26.1 years.

With the subjects in a nonfasting state, blood was drawn from the antecubital vein in sterile vacuum tubes and allowed to clot, and the serum was separated by centrifugation. Serum studies consisted of the determination of the total protein-bound hexose,[3] cholesterol,[4] total lipids,[5] and protein fractionation by paper electrophoresis.[6] A Spinco Model R electrophoresis system was employed with use of a Durrum-type plastic cell and an automatic

Fig. 2 (Patient 3).—Necrobiosis lipoidica diabeticorum present four years.

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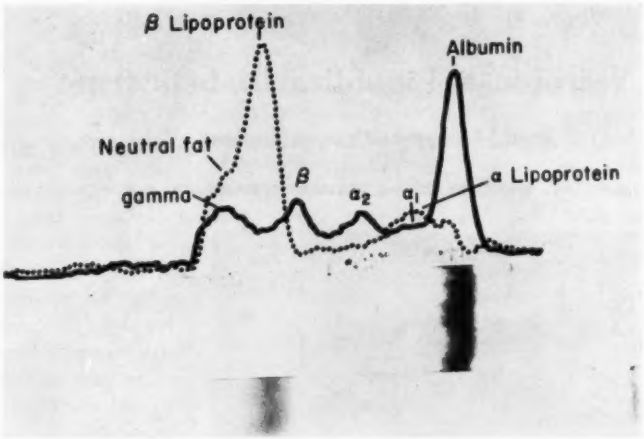

Fig. 3.—Serum protein and lipoprotein electrophoretic patterns of Patient 3.

recording densitometer, the Spinco Analytrol. After protein separation, bromphenol blue was used to stain the serum proteins, oil red O was used to stain the lipoprotein fractions,[7] and a modified periodic acid-Schiff stain (PAS) was used to demonstrate glycoproteins.[8] Figure 3 illustrates typical serum protein and lipoprotein electrophoretic patterns of one patient with necrobiosis lipoidica diabeticorum. Figure 4 compares a PAS-stained serum electrophoretic strip of Patient 3 with that of a control serum. Glucose-tolerance tests were done on all patients. Serum viscosities were done with Ostwald 100 viscosimeters at temperatures ranging from 37 C to 30 C. The urinary levels of 17-ketosteroids[9] and 17-hydroxycorticoids[10] were obtained. Biopsy specimens were fixed in formalin and stained with Masson I, hematoxylin and eosin, and diastase-PAS. Controls for the protein electrophoretic fractionations consisted of 32 male blood donors and 25 female student nurses. Fifty-nine blood donors and hospital personnel were controls for the total lipids and lipoprotein fractions. The ages of these controls ranged from 19 to 46 years, with a uniform distribution throughout each 10-year age group.

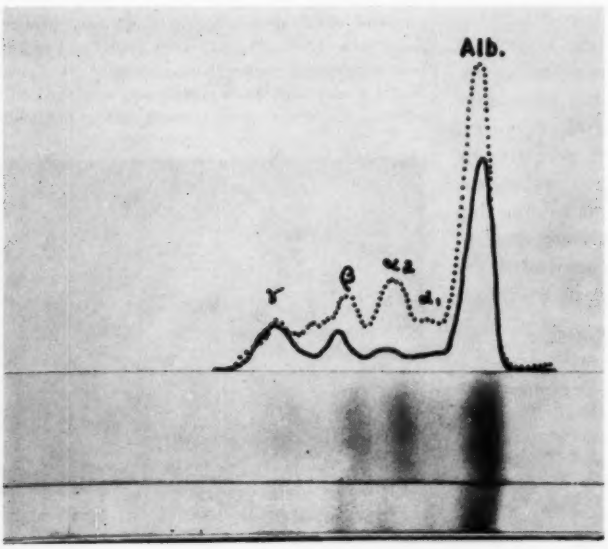

Fig. 4.—PAS-stained electrophoretic pattern of a normal control serum compared with serum of Patient 3.

TABLE 1.—*Lipid Metabolic Studies of Eight Patients with Necrobiosis Lipoidica Diabeticorum*

	Patients							
	1	2	3	4	5	6	7	8
Cholesterol, mg. %	160	228	232	239	238	204	159	256
Total lipids, mg. %	542.7	673.3	661.3	673.3	686.0	616.3	904.8	914.3
Lipoproteins, %								
Neutral fat	28.8	26.3	15.0	26.3	32.8	14.5	28.4	14.3
β-Lipoprotein	41.4	57.0	60.0	44.7	52.3	71.0	56.8	57.1
α-Lipoprotein	29.8	16.7	25.0	29.0	14.9	14.5	14.8	28.6

Results

Lipid Metabolism.—The total lipids were elevated above the mean normal in two patients; however, the cholesterol and distribution of the lipid fractions in each were normal. No abnormalities of lipid metabolism were present in any of the remaining patients. Table 1 gives the results of all lipid studies, and Table 2 compares the mean values of these patients with the mean values of the control group of 59 patients

TABLE 2.—*Mean Values of Lipid Studies in Eight Patients with Necrobiosis Lipoidica Diabeticorum Compared with Mean Values of Fifty-Nine Controls*

	Patients' Mean	Controls		
		Mean	Standard Deviation	Standard Error
Cholesterol, mg. %	214.5	244.6	34.3	5.2
Total lipids, mg. %	709.0	575.3	103.1	13.7
Lipoproteins, %				
Neutral fat	23.3	26.4	8.4	1.7
β-Lipoprotein	55.04	48.9	13.2	2.3
α-Lipoprotein	21.66	24.9	8.6	1.5

Serum Viscosity.—Both pooled normal sera and sera of the patients increased in viscosity with decreasing temperature. The mean skin temperature of the lower extremity ranges from 32.35 C at the knee to 30.20 C at the sole.[11] The lesions of necrobiosis lipoidica diabeticorum occur most commonly in this general area, where the skin temperatures are lowest. The results shown in Table 3 reveal that the percentage increase in viscosity of the patients' sera was greater than that of the normal in the critical temperature range from 32 C to 30 C.

TABLE 3.—*Serum Viscosity of Six Patients Compared with a Pooled Serum Control at Varying Temperatures*

Patient	Rate of Flow Through Viscosimeter, Sec.			Increase in Viscosity, %	
	Internal, 37C	Knee, 32C	Sole, 30C	Internal to Knee	Knee to Sole
1	69.5	78.0	82.0	17.9	5.1
2	103.0	113.5	119.5	16.0	5.2
3	102.0	113.0	120.0	17.6	6.1
4	90.0	99.0	114.5	27.2	15.6
5	78.5	87.5	91.5	16.5	4.5
6	93.5	100.5	105.0	13.3	4.4
Patient average	89.4	98.6	105.4	17.8	6.8
Normal pooled serum	93.0	107.0	110.0	18.2	2.8

Urinary Steroids.—The 17-ketosteroids and 17-hydroxycorticoids were normal in the two patients studied. Values for the 17-ketosteroids in these two patients were 10.96 mg/24 hours and 14.00 mg/24 hours.

TABLE 4.—*Serum Protein Studies of Eight Patients with Necrobiosis Lipoidica Diabeticorum*

Patient	Albumin		α_1		α_2		β		γ	
	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.
1	39.8	2.78	7.1	0.49	15.1	1.05	18.2	1.27	19.8	1.38
2	37.8	2.61	7.5	0.52	12.7	0.88	18.0	1.24	24.0	1.66
3	38.8	2.79	8.0	0.56	15.3	1.10	18.2	1.31	19.7	1.42
4	41.2	2.97	7.1	0.51	13.6	0.98	14.4	1.03	23.7	1.70
5	61.3	5.09	3.5	0.29	7.5	0.62	15.6	1.29	12.1	1.00
6	53.6	4.13	0.3	0.23	7.3	0.56	19.0	1.46	19.8	1.52
7	48.4	3.48	6.3	0.45	8.6	0.62	14.5	1.04	22.2	1.60
8	58.6	4.57	4.6	0.36	10.1	0.79	12.9	1.00	13.8	1.07

TABLE 5.—*Mean Values of Serum Protein and Total Protein-Bound Hexose of Eight Patients and Fifty-Seven Controls*

	Patients' Mean	Controls		
		Mean	Standard Deviation	Standard Error
Total protein, gm.	7.41	7.00	--	--
Albumin, gm.	3.50	3.39		
Albumin, %	47.44	48.40	5.5	0.24
Globulin				
α_1, gm.	0.41	0.40		
α_1, %	5.55	5.80	1.3	0.23
α_2, gm.	0.84	0.77		
α_2, %	11.28	11.00	2.4	0.35
β, gm.	1.21	1.27		
β, %	16.35	18.10	3.9	0.69
γ, gm.	1.44	1.20		
γ, %	19.39	17.20	4.5	0.31
Total protein-bound hexose, mg. %	159.9	110.80	7.2	1.90

Values for the 17-hydroxycorticoids were 2.66 mg/24 hours and 6.21 mg/24 hours.

Serum Proteins.—Four of the patients revealed an elevated α_1- and α_2-fraction and a decrease in albumin. The β-fraction of Patient 8 was 12.9%, whereas the β- and γ-fractions of all other sera were within normal limits. The results are summarized in Table 4. The mean values are compared in Table 5 with mean control values from 57 normal persons.

Carbohydrate Metabolism.—Patient 4 was noted to have a diabetic glucose-tolerance curve. This patient had repeatedly normal fasting glucose levels. Patients 5 and 7 were found to have curves suggestive of diabetes mellitus, with an elevation of the two-hour glucose values. Patient 6 was noted to have a flat glucose-tolerance curve coupled with a very low total protein-bound-hexose level. The significance of these findings is not known at present. These data are in Table 6.

Those patients having elevated α-proteins also had markedly elevated total protein-bound-hexose levels. These data are given in Table 6, and the mean values are compared with the mean values of 47 normal patients in Table 5.

Table 7 shows the percentage distribution of the PAS-positive material associated with the serum protein fractions. This reveals an elevated α_2-fraction in six of the eight patients, and it can be noted that this occurs independently of an elevation of the total protein-bound hexose. The albumin fraction, though lower than the control, is still higher than many reported values. This may be due to the fact that the low-temperature ethanol fractionation method was not employed before serum electrophoresis.[12]

Histology.—A histological section from each of the patients revealed a typical picture of necrobiosis lipoidica diabeticorum (Fig. 5). Varying degrees of abnormalities, from slight intimal proliferation to occlusion, were observed in the blood vessels (Fig. 6). The involved vessels included superficial capillaries as well as the larger vessels deep in the dermis. This material obstructing the lumina of the vessels stained blue with the Masson trichrome stain (Fig. 7) and was PAS-positive after diastase digestion to remove the glycogen (Fig. 8). This strongly suggests that the material is composed principally of a complex carbohydrate.[13]

TABLE 6.—*Glucose-Tolerance Tests in Eight Patients with Necrobiosis Lipoidica Diabeticorum*

Patient	Total Protein Bound Hexose	Glucose, Mg. per 100 cc.				
		Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.
1	244	82	106	109	82	71
2	222	93	143	118	87	72
3	247	83	90	130	115	60
4	233	117	173	205	164	144
5	115.2	121	190	153	127	120
6	62.6	90	95	80	75	70
7	88.1	81	131	144	130	113
8	67.9	92	128	124	115	90

Comment

Many conflicting concepts of the etiology of necrobiosis lipoidica diabeticorum have been advanced. It has been postulated that a general disturbance of lipid metabolism

TABLE 7.—*Percentage Values of Serum Fractions Stained with Periodic Acid Schiff*

Patient	Albumin	α_1	α_2	β	γ
3	44.3	7.6	16.8	18.4	12.9
2	48.4	5.8	7.8	14.7	23.3
4	47.4	4.2	12.7	18.9	16.8
1	25.4	4.5	9.8	17.7	42.6
7	43.3	8.0	16.8	13.3	18.6
8	44.3	4.6	20.9	18.6	11.6
6	38.1	9.5	16.6	15.7	20.1
5	31.2	7.4	14.9	17.8	28.7
Patient mean	40.5	6.5	14.5	16.9	21.8
Control	58.2	5.5	7.7	11.0	17.6

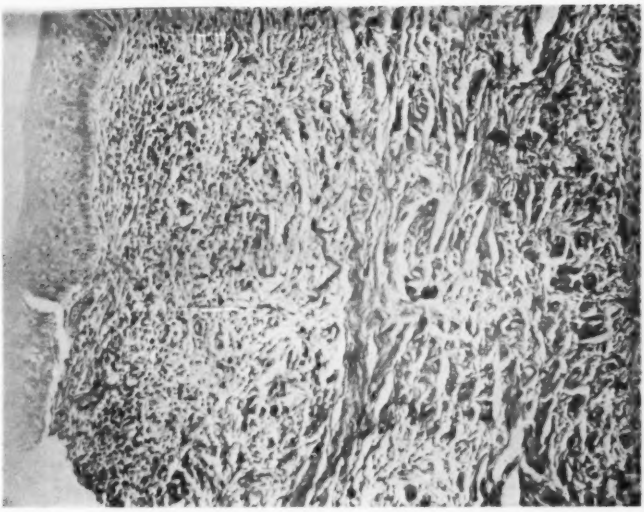

Fig. 5. — Necrobiosis lipoidica diabeticorum; hematoxylin and eosin.

may be the etiologic factor.[14] Urbach,[15] in the first description of necrobiosis lipoidica diabeticorum, remarked on the severity of the vascular lesions and postulated that they were caused by a circulating toxin due to diabetes mellitus. Vascular lesions of varying degrees have commonly been noted,[16,17] with many investigators believing the cause of the lesion to be primarily a vascular one.[18-21] Some authors have associated the lesions of necrobiosis lipoidica diabeticorum with severe diabetes or poor diabetic control. Others have shown that the duration, severity, or control of the diabetes did not seem to have any relationship to the disease process.[2,18,22,23] The increase in frequency of reports in the literature of necrobiosis lipoidica diabeticorum occurring in nondiabetics[24-26] has resulted in attempts to change the name.[27] It is obvious that the common denominator, if such exists between diabetes mellitus and necrobiosis lipoidica diabeticorum, cannot be the hyperglycemia or hypoinsulinism.[24,25]

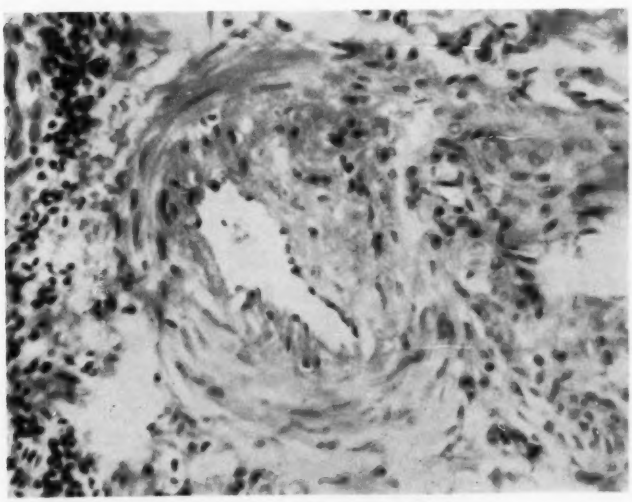

Fig. 6. — Hematoxylin-and-eosin stain of a large dermal vessel, showing hyaline material partially occluding the lumen.

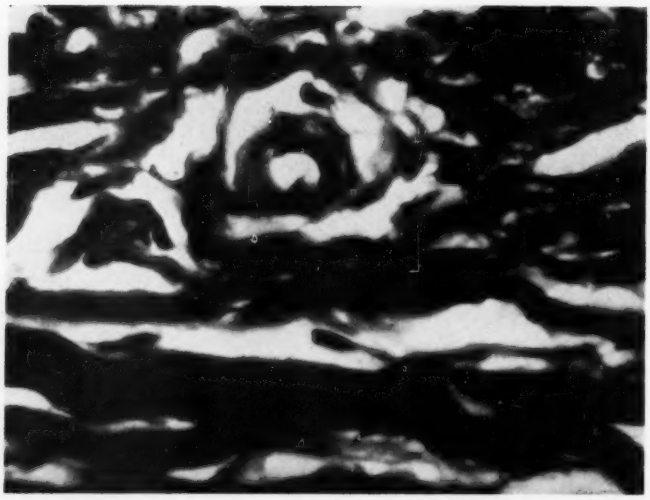

Fig. 7. — Masson trichrome stain of small vessel in upper dermis, showing intense staining of material in thickened wall and in the lumen.

Several factors prompted us to investigate the pathogenesis of the blood vessel changes. The coexistence of necrobiosis lipoidica diabeticorum and Kimmelstiel-Wilson syndrome has been reported.[28] Vascular lesions are found in both necrobiosis lipoidica diabeticorum and complicated diabetes mellitus.

Frequent reports have shown that in diabetes mellitus with vascular complications there is an elevation of the total protein-bound hexose.[29,30] This protein-bound carbohydrate lies mainly in the α_2-globulin fraction of the serum.[29,31] *The level of the protein-bound hexose has been found to be independent of the level of the blood glucose.*[29-31] Many investigators have been able to correlate the rise of the total protein-bound hexose and of the α_2-glycoprotein with the increase in the vascular complications of diabetes mellitus.[29,31,33] Berkman[32] noted significant rises in these serum constituents only when clinically detectable vascular disease was present. Ditzel

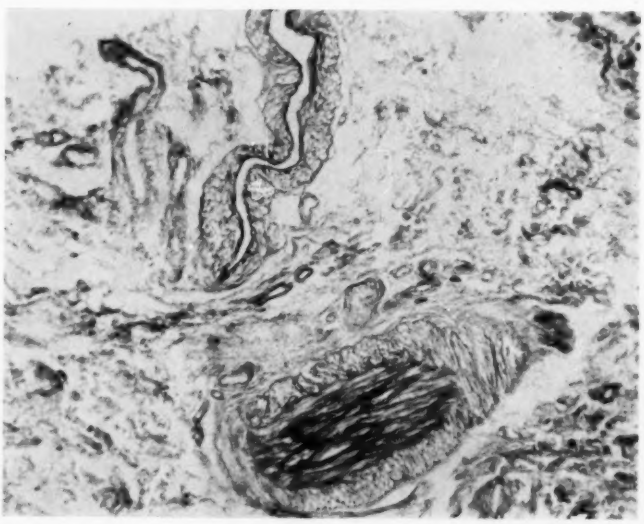

Fig. 8. — Complete occlusion of large dermal vessel with material staining PAS-positive after diastase digestion.

and Moinat [33] noted an associated rise in the α_2-glycoprotein in pregnant diabetics with the occurrence of vascular changes in the small blood vessels. These abnormalities consisted of arteriolar constriction, intra-arteriolar sludging of the red blood cells, and slowing of the linear velocity of flow and exudation. The process of exudation was followed by edema and hyalinization. Following parturition, when the level of the α_2-glycoprotein fell to normal values, these pathological vascular changes reverted to normal. LeCompte [34] and Gilliland et al.[31] suggested that the vascular lesions of diabetes mellitus may be due to the deposition in the vessels of constituents of the blood plasma, such as the protein-bound polysaccharide. They noted that the hyaline material in the damaged vessels gave a positive PAS reaction. Nichols, Moinat, and Tuller [35] were unable to produce vascular lesions in alloxan-diabetic rats with uncontrolled diabetes. They found the level of the α_1-globulin and α_1-glycoprotein lower than the control values in the same animal before it was made diabetic. They postulated that the lowering of the plasma levels of the α_1-globulin fraction may prevent the development of hyaline vascular disease, whereas elevation of the α_2-globulin may be responsible for the production of the vascular lesion of human diabetes.

The results of our studies on lipid metabolism and urinary steroid excretion revealed no abnormalities. This is in agreement with those who believe that the fatty infiltration in the lesions of necrobiosis lipoidica diabeticorum is a secondary phenomenon.[16,19]

These studies revealed a marked elevation of the total protein-bound hexose, an elevation of the α_2-globulin and, in all instances, a diastase-resistant PAS-positive material in the damaged vessels.

Electrophoretically, there was an elevation in the serum α_2-glycoprotein, as determined by the PAS reaction. This was observed with or without an elevation of the total protein-bound hexose. These abnormalities, reported by others in patients with the vascular complications of diabetes mellitus, occur in both the diabetic and the nondiabetic patients of this series. This emphasizes that the production of the vascular lesion is not dependent on hyperglycemia.

A tentative mechanism of the development of the lesions of necrobiosis lipoidica diabeticorum may now be postulated. There occurs in these patients an elevation of the protein-bound-carbohydrate fractions of the serum above the levels reported in diabetes mellitus with vascular complications. This may be present in diabetes mellitus or in nondiabetic patients. There occurs, as a result, constriction of arterioles, dilatation of venules, slowing of the blood flow with sludging of the formed elements, and exudation of plasma. This may lead to edema and deposition of a PAS-positive hyaline material, with resultant vascular occlusion and necrobiosis.

There are still other factors influencing this process. The lower extremity, the region usually involved in necrobiosis lipoidica diabeticorum, has a low skin temperature. Normally a low temperature tends to cause arteriolar constriction and an increase in plasma viscosity. In necrobiosis lipoidica diabeticorum there is a further increase in serum viscosity at the skin temperature of the lower extremity. A factor that may be responsible for the commoner occurrence of necrobiosis lipoidica diabeticorum in females is possibly the constant exposure of their lower extremities to all extremes of temperature.

Multiple factors may therefore be present, all tending to produce conditions allowing for the deposition of a carbohydrate-containing material from the plasma gradually occluding the vessels, with subsequent necrobiosis. Fat and glycogen are deposited secondarily in the areas of necrobiosis.

Summary

A histochemical, biochemical, and electrophoretic study of eight cases of necrobiosis lipoidica diabeticorum is reported.

An elevation of the total protein-bound hexose, α_2-globulin, and α_2-glycoprotein is shown to be present with or without diabetes mellitus.

There is a diastase-resistant PAS-positive material in the damaged vessels.

Viscosity of the serum of patients with necrobiosis lipoidica diabeticorum is greater than that of normal serum at the normal skin temperature of the lower extremity.

No abnormalities of lipid metabolism or urinary steroid excretion were noted.

A hypothesis for the formation of the lesions of necrobiosis lipoidica diabeticorum is advanced. The production of the vascular lesion in diabetes mellitus may depend on a similar mechanism.

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Skin Manifestations of Organic Phosphate Insecticide Poisoning

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Fatalities due to organic phosphate insecticide poisoning establish undeniable evidence of a relatively new and often baffling menace to public safety. If such tragedies, often occurring within minutes of the onset of symptoms,[1] are to be avoided, the physician must be aware of the manifestations of this disease, particularly before signs of cardiac arrest, acute abdomen, convulsions, or coma supervene. In the following case report, a dermatological finding is presented as a sign of chronic exposure to parathion, one of the more commonly used organic phosphate insecticides.

Report of a Case

The patient was a 25-year-old fireman complaining of periodic profuse sweating of the arms and back associated with mild pruritus of three weeks' duration. He had been well until he noted the onset of drenching hyperhidrosis occurring at work as well as at home. Roughness of the skin and mild pruritus followed. He revealed that in addition to his usual occupation as a fireman he had been engaged in spraying parathion for the past three months. Two weeks previously, two of his associates had been hospitalized with nausea and vomiting. One week previously, the patient had been examined and found to be well. He was referred for dermatological consultation because of unexplained hyperhidrosis.

Examination revealed a well-developed well-nourished white man, appearing his stated age of 25. Goose flesh (cutis anserina), manifested by closely set papular elevations surmounted by hairs, was noted extending across the entire upper posterior thorax and over both upper arms. Areas of localized hyperhidrosis appeared on the dorsum of the arms and over the scapulae. Pupils appeared dilated, although they reacted to light and in accommodation. There were no other abnormal findings.

The patient was advised to discontinue handling parathion. Within two weeks, hyperhidrosis subsided completely. The goose-flesh appearance of the skin began to involute during the third week and had disappeared completely in four weeks.

Review of Literature

The organic phosphates[2,3,9] responsible for human poisoning are listed below with their common trade names and chemical structures.

1. Parathion — O,O-diethyl-O-*p*-nitrophenyl thiophosphate
2. Systox — O,O-diethyl O-ethylmercaptoethyl thiophosphate
3. TEPP — tetraethylpyrophosphate
4. HETP — hexaethyltetraphosphate
5. EPN — ethyl *p*-nitrophenyl thionobenzene phosphate
6. OMPA — octamethyl pyrophosphoramide
7. Malathion — O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate
8. Diazinon — diethyl-2-isopropyl-4-methyl-6-pyrimidythionophosphate

Most reported fatalities have been from the more commonly used preprations, parathion and Systox. Diazinon is readily absorbed through the skin and may prove to be very toxic. Malathion exhibits low toxicity as compared with the others. All of these compounds are listed in Toxicity Classes 5 and 6, extremely toxic and supertoxic,[8] respectively.

The formulations[2] consist of 3% sprays, 4% dusts, and 10% aerosols. Persons exposed include those engaged in the manufacturing process as well as home gardeners, exterminators, and orchard sprayers. The discarded chemical container has sufficient residual poison to be regarded as a menace to children, in whom ingestion has proven fatal. Absorption through the skin

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From the Division of Dermatology, Department of Medicine, University of Miami School of Medicine.

is another important route of poisoning. Because these compounds have very low vapor pressure, inhalation alone may not lead to serious poisoning. Once absorbed, however, their mode of action involves inhibition of cholinesterase enzymes of the blood and tissues, resulting in release and accumulation of excessive amounts of acetylcholine. Such activity causes the following symptoms and signs[1]: headache, weakness, nausea, vomiting, cramps, giddiness, blurred vision, diarrhea, chest discomfort, nervousness, sweating, miosis or paradoxical mydriasis,[4] salivation, tearing, cyanosis, pulmonary edema, muscle twitches, convulsions, coma, areflexia, and loss of sphincteric control.

The essential finding for laboratory diagnosis is the marked reduction of the cholinesterase level of blood or serum. The mean cholinesterase values of normal persons not exposed to phosphate insecticides[5] range as follows. RBC, 0.67 to 0.86 pH units per hour; plasma, 0.70 to 0.97 pH units per hour. Levels of 0.5 or less for either cells or plasma indicate abnormal cholinesterase depression, although signs or symptoms may not be present in some persons until 0.2 has been reached. In addition to the cholinesterase level, *p*-nitrophenol determination of urine may be done as a measure of parathion exposure. The electrocardiograph may show AV block, bradycardia, or exaggeration and inversion of the T-wave with disappearance of the P-wave.

Necropsy findings are sparse. Sections of the respiratory tract reveal hyperactivity of serous and mucous glands. Other changes appear secondary to pulmonary or cerebral edema or convulsions.

The differential diagnosis runs the gamut of cardiac as well as acute abdominal diseases. Poisonings have been confused with heat stroke, heat exhaustion, gastroenteritis, and pneumonia. Mild poisoning must be differentiated from asthma and simple fright. In every case there is need for a careful history of exposure and a comprehensive analysis of clinical observations.

Therapy[1,6,7] is directed toward overcoming the adverse effects of excessive acetylcholine. Atropine, therefore, is the drug of choice and is administered only after cyanosis is overcome by artificial respiration or positive-pressure breathing. One to two milligrams ($\frac{1}{60}$ to $\frac{1}{30}$ grain) of atropine sulfate, every hour, is given intravenously, up to 20 mg. per day. Although such doses appear excessive, persons poisoned by organic phosphates have been noted to have increased tolerance for atropine. The effects of intravenously administered atropine begin in one to four minutes and are maximal in eight minutes. The skin becomes dry and blushed. Tachycardia may be present. Atropinization, to less degree, should be maintained in all cases for 24 hours and in severe cases for 48 hours. *Morphine, theophylline, theophylline-ethylenediamine,* or *intravenous fluids* are contraindicated. After signs and symptoms have been allayed, the patient is decontaminated in an alkaline (baking soda) bath. The acute emergency lasts 24 to 48 hours, and the patient must be watched continuously.

Summary and Conclusions

Insecticides of organic phosphorous derivatives are highly dangerous poisons to which adults and children are being exposed. The commonest offenders are parathion and Systox, used as garden insecticides. Physicians should be on guard for the occasional patient with clinical signs of parasympathetic stimulation as the key to a diagnosis of chemical poisoning. Signs include miosis, paradoxical mydriasis, localized hyperhidrosis, salivation, tearing, cyanosis, pulmonary edema, muscle twitches, convulsions, coma, areflexia, and loss of sphincteric control. Goose-flesh appearance of the skin has been observed as a further aid in diagnosis. All of these foregoing changes are reversible with prompt and adequate therapy. Atropine is the therapeutic drug of choice.

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Multiple Large Tumors of Granular-Cell Myoblastomata of the Skin

Report of a Case

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Granular-cell myoblastoma is a tumor which is rarely encountered in the skin. Of the reported cases, 33% have occurred in the tongue; only about 20% of these tumors have been found in the skin.[1] This tumor has, however, been observed in various organs, including the external auditory meatus, the bronchi, the common bile duct,[2] the maxilla, the parotid gland, the larynx, the orbit, the heart, the esophagus, the bladder, the urethra perineum, the anal region, and the ovary. Characteristically, it is a slowly growing, nondistinctive, sessile or pendunculated asymptomatic nodule which is usually solitary and which may eventually ulcerate. Paroxysmal pain has been a symptom in some patients. Multiple lesions are the exception rather than the rule. Malignant alteration with metastases may occur on rare occasions.[3] It is difficult to classify malignant granular-cell myoblastoma. There are some who feel that it is malignant *de novo*. Histologically, the tumor is composed of ribbons of large polyhedral cells with small round vesicular nuclei and a pale cytoplasm with acidophilic granules.[4] Pseudoepitheliomatous hyperplasia is usually present.

Histogenetically, this tumor is now believed to be of neural origin, although at one time it was considered to be a tumor of immature striated muscle. A myoblastic origin of this tumor was postulated because in lesions of the tongue cells which appeared to be transitional between tumor cells and muscle fibers were sometimes seen.[5] Also, some observers have described cross striations which are suggestive of myofibrils. However, the evidence for a neural origin seems to be strong in view of the following observations[6-8]: 1. Granular cells are occasionally seen arranged concentrically around a core of bundles of axis cylinders. 2. Groups of granular cells have been found within nerve sheaths both within and in the vicinity of the tumor. 3. The cells have a slight affinity for fat stains.

Histologically, one may have to distinguish granular-cell myoblastoma from xanthoma on first glance. This should not be difficult, because the xanthoma cells are foamy and not granular. Moreover, xan-

Fig. 1.—Ulcerated tumor in pubic area.

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From the Department of Dermatology of the University of Cincinnati College of Medicine.

Fig. 2.—Tumor on left forearm.

thoma cells take on fat stains with avidity. An important differential point is the pseudoepitheliomatous hyperplasia of the epidermis overlying a granular-cell myoblastoma. In the case of xanthoma, the overlying epidermis is usually atrophic.

A 49-year-old Negro woman was admitted to the Cincinnati General Hospital on Aug. 10, 1955, for a sore just above her pubic region. She first noticed a lump in her skin about 14 years prior to admission. This had gradually increased in size till ulceration occurred a year prior to admission. A lump on her left shoulder had also been present for 14 years. Three years ago she developed a lump on her left forearm. She said that she had developed a lump on her right upper arm recently.

Her past history revealed a panhysterectomy for pelvic inflammatory disease in 1917, a lung abscess in 1936, chronic cholecystitis and cholelithiasis in 1937, and tonsillectomy in 1937. Physical examination revealed a rather obese, slightly lethargic female in no apparent distress or discomfort.

The skin showed the following lesions: 1. An ulcerated hard skin tumor 2×3 cm. was in the

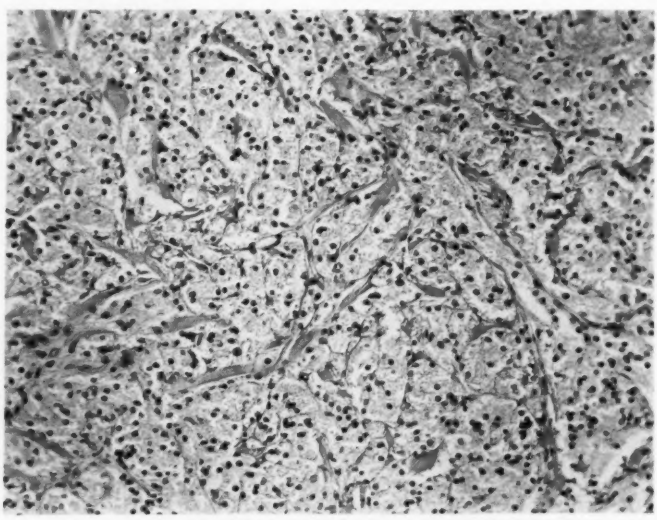

Fig. 3.—Photomicrograph showing typical granular cells; reduced about 23% from mag. × 160.

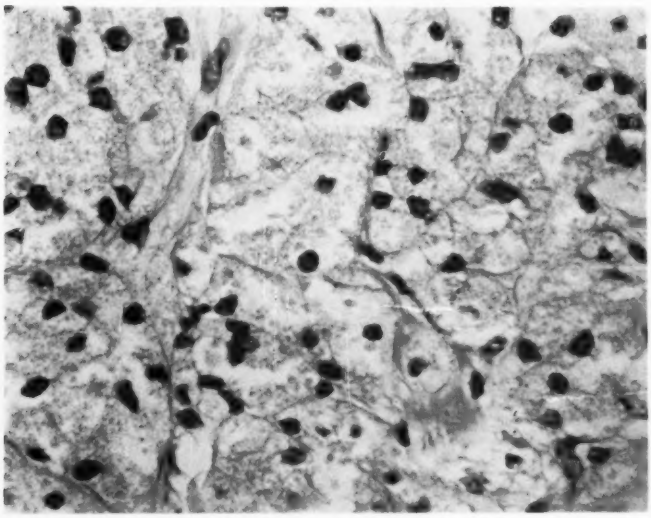

Fig. 4.—Photomicrograph; reduced about 23% from mag. ×650.

suprapubic region. 2. A tumor 4×5 cm. was in the left scapular region, with hyperpigmented and verrucous overlying epidermis. 3. A nodule was on the flexural surface of the left forearm. 4. A nodule with verrucous surface was on the lateral aspect of the right upper arm.

Her other systems were normal. Laboratory investigations showed a normal hemogram and urinalysis and nonreactive serological tests for syphilis. Bacteriological studies of the ulcerated lesion produced Proteus mirabilis from the surface exudate.

A chest x-ray revealed increased bronchovascular markings. A hiatus hernia was discovered on upper gastrointestinal series. Findings on biopsies of the lesions in the suprapubic left scapular and left forearm regions revealed typical granular-cell myoblastoma.

Resection of the suprapubic and left forearm tumors was performed by the Department of Surgery. The patient refused extirpation of the lesion on her left shoulder.

This case is reported because of the occurrence of multiple fairly large tumors of the skin. Clinically the large-sized ulceration was suggestive of skin sarcoma in spite of the history of long duration. None of these was malignant, histologically, despite the fact that two of them had been present for 14 years. The clinical diagnosis of granular-cell myoblastoma was not made. Three cases have been observed in the department recently. An attempt was made by inspection and skin microscopy to determine if verrucous pseudoepitheliomatous hyperplasia were present. This was found to be of no clinical value in differentiating between subepidermal nodular fibrosis and granular-cell myoblastoma of the skin. These latter tumors are radioresistant, and the treatment of choice is surgery.

Summary

A case is reported of multiple large-size granular-cell myoblastoma of the skin. The diagnosis was not made clinically.

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Pityriasis Rubra Pilaris with Strange Localization

Report of a Case

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Figure 1

A 41-year-old white man had a skin condition of six years' duration. There was nothing unusual except the localization: numerous distinct follicular lesions, each separated from the others by normal skin, formed a ring at the outside of the lower part of the thorax and the abdomen. Inside this ring the skin was normal. Only a few isolated follicular lesions were seen below the navel toward the mons veneris, suggesting the male type of pubic hairiness, but there were no pubic hairs in the center of the hyperkeratotic lesions. The inguinal regions were richly covered with typical lesions circling upward as a thin band to the lower arch of the ribs. Otherwise, the skin of the body was normal. The clinical diagnosis was pityriasis rubra pilaris. This was confirmed by the histopathological findings of Dr. B. S. Kline: "There is hyperkeratosis especially at the hair follicles. Moderate acanthosis. The stratum granulosum is enlarged, the stratum corneum is thicker than normal. The basal cells are more differentiated and with prominent intracellular bridges. The cellular infiltration consists mostly of lymphocytes and is located around the blood vessels. In the dermis there are fairly numerous sudoriferous glands and granulomatous tissue with numerous lymphocytes present, epitheloid and fibroblastic cells. The lesions somewhat circumscribed, in places appear miliary. In one of the sections there are areas unrelated to the granulomatous lesions in which the epidermis is somewhat heaped up, the basal cells contain abundant brown pigment. Examination of the apparently earliest granulomatous lesions together with the regional epidermis still showing epithelial prolongations, suggests that the process is primary in the dermis and that the epidermis is secondarily involved. Final diagnosis:

Figure 2

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The lesion is compatible with the clinical diagnosis of pityriasis rubra pilaris."

The intriguing question was as follows: What is the cause of this strange localization? I have never seen a similar case in nearly 50 years of dermatological practice. I could not think of an explanation until I recently saw a baby in his crib sleeping on his belly! It is possible that in this position (1) there is more sweating from the skin of the abdomen because of the close contact with the sheet, making a keratinization which is always accompanied by dryness less probable; it is also possible that (2) the constant pressure prevents the formation of the hyperkeratotic plugs.

My hunch proved to be true; the patient usually slept on his stomach.

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Molluscum Contagiosum of the Buccal Mucosa

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Molluscum contagiosum is usually seen on the skin. An instance of involvement of the eyelids, close to the conjunctiva, is recorded by Blank,[1] with an excellent illustration by Ronchese. As far as I know, there is no report of molluscum contagiosum of the mucous membrane.

Submitted for publication Jan. 16, 1958.

From the Department of Dermatology, Boston University School of Medicine (Herbert Mescon, M.D., Professor). Assistant Professor of Dermatology.

Molluscum contagiosum involving the buccal mucous membrane.

A 43-year-old white woman was seen, complaining of a bleeding tumor of the mouth of three weeks' duration. She stated that the lesion had been present for about seven months but had caused no discomfort.

Examination revealed a nodular lesion involving the vestibular surface of the lower labial mucosa, measuring 1.5 mm. in diameter, with firm consistency. The surface was hemorrhagic, and the surrounding mucosa showed superficial purulent discharge. The rest of the body revealed no abnormalities.

A tentative diagnosis was made of an infected mucous cyst or granuloma pyogenicum. Pathological examination proved it to be molluscum contagiosum.

This case demonstrates the importance of performing biopsies on all lesions, regardless of clinical diagnosis.

351 Armistice Blvd.

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Cheilitis—Unusual Manifestation Due to Solar Sensitivity

Report of a Case

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In June, 1957, I saw a 43-year-old woman with a history of severe cheilitis of several months' duration. There were marked peeling of the lips and fissures in the corners of the mouth, which made it difficult to open the mouth. This condition would improve at times but never cleared completely.

The patient had had vitamins, hydrocortisone (Hydrocortone) ointments, patch tests with lipsticks, and change of toothpaste, with no relief.

I treated her with a mixture of cortisone (Cortone) and nystatin (Mycostatin) ointment, gave her medication for a mild scalp seborrhea, and patch-tested her with the filter of the cigarette she had been smoking. She failed to improve.

In the course of our conversation, she described a "nerve" pill she had been taking for some months which was recognized as chlorpromazine (Thorazine). I suggested another sedative, and she said that I should give her one that *she could chew* because of her inability to swallow pills.

She was patch-tested on the upper outer aspect of an arm with a crushed chlorpromazine tablet on cellophane (Scotch) tape, and in 48 hours there was a mild positive reaction. She called the day after the test was removed and said that she had a large blister at the site of the test. Also, her lips were better.

At my suggestion, she chewed another chlorpromazine tablet a few weeks later, and the condition was promptly reproduced, only after exposure to sunlight.

Conclusion: Chlorpromazine can cause a local solar sensitivity.

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108 Scott St.

Synthetic Urine as a Local Therapeutic Agent in Dermatology

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According to tradition, one's urine is an efficacious remedy for chapped hands. Folklore also emphasizes the virtues of the frequent application of a young infant's wet diaper in the management of acne. So many people have faith in this remedy that it was deemed worth while to evaluate the product critically.

Memories of four years in medical school with the almost constantly present 5-gal. bottle and funnel in the men's lavatory suggested a ready source for this natural secretion, but esthetic factors and discretion recommended some other origin. It was finally determined to employ a synthetic urine based upon the average composition of the natural product. "Dorland's Illustrated Medical Dictionary" states that 1000 parts of healthy urine contain about 960 parts of water and 40 parts of solid matter, which consists chiefly of urea, 23 parts; sodium chloride, 11 parts; phosphoric acid, 2.3 parts; sulfuric acid, 1.3 parts; uric acid, 0.5 parts, and also hippuric acid, leukomaines, urobilin, and certain organic salts. With this information at hand, I prepared an aqueous solution, containing urea, 2.3%; sodium chloride, 1.1%; phosphoric acid, 0.23%, and sulfuric acid, 0.13%, and dubbed this solution Lotion K in honor of its usual source, the kidney.

Lotion K was first prescribed to a group of student nurses who exhibited acne of various types and severity. It was applied freely three or four times a day. No other agent of any type was suggested or even mentioned. The results were equivocal. Some patients saw improvement; others did not. Since these girls were being observed weekly, a psychic factor may have been operative. All in all, the results warranted further investigation. Accordingly, Lotion K was prescribed for a number of feebleminded patients

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with acne at a state school, with the thought that this type of patient would be less susceptible to psychic effects. After two months, an elderly physician on the staff was asked his opinion about my new prescription for acne, whose formula he did not know. Better known for his frankness and honesty than his tact and using the vernacular effectively, he suggested I would have done as well had I urinated on the patients with acne. With this canny observation, the application of Lotion K for acne was brought to an end.

In the meantime, urea, salt, phosphoric acid, and sulfuric acid in the proportions found in urine were being used as compresses and in lotions and ointments for various inflammatory conditions of the hands. Improvement occurred in many cases, but, in brief, the results obtained were not superior to those resulting from the use of other long-established remedies.

Lotion K was tried in many other dermatological entities, but its use has been continued in only one condition. Half-strength Lotion K, applied as compresses to dirty leg ulcers, is more effective in producing a clean wound with healthy granulation tissue than the other remedies, including high-priced specialties, that have been employed in our department. As a rule, compresses with half-strength Lotion K are applied during the waking hours. At bedtime, the dressings are removed and a cradle with a 15 to 25 watt electric bulb is placed over the uncovered legs. Odor and discharge disappear rapidly, and the ulcer assumes a healthy appearance.

Summary

Tradition ascribes a healing role to urine in certain dermatological conditions, notably acne and dermatitis of the hands. Clinical observations with a "synthetic urine" demonstrated that it was of no value in acne. Some hand cases improved on "synthetic urine," but the results were not superior to those obtainable with other medicaments. It was only in necrotic leg ulcers that this remedy showed superiority. Half-strength synthetic urine excels as a compress for chronic ulcers of the legs, producing results superior to other remedies including high-priced specialties.

411 Walnut St.

Tellurium Dioxide Suspension in the Treatment of Seborrhea Capitis

ELMER R. GROSS, M.D., Wilmington, Del., and CARROLL S. WRIGHT, M.D., Philadelphia

Placed as they are within a family group in the periodic table, the four elements, oxygen, sulfur, selenium, and tellurium, are generally known to be related in their chemical properties.[1] Additionally, it has been demonstrated within recent years that sulfur and selenium[2] possess related therapeutic properties which are of particular value to the dermatologist in his treatment of seborrhea capitis.

In consideration of the long history of sulfur as an effective agent in the treatment of dermatoses and of the proof through investigation of the value of selenium compounds,[3] it was deemed wise to assume that compounds of tellurium might have similar therapeutic application.

During the past four years a standard 2.5% suspension of tellurium dioxide in a suitable shampoo vehicle has been used in intensive clinical studies. Safety tests[4] were carried out on laboratory animals, and excretion studies[5] on human urine were made by determining the tellurium content before and after treatment with tellurium dioxide shampoo. The results of these tests follow.

Laboratory Studies

Comprehensive laboratory studies* were made using 20 animals (guinea pigs, rabbits, and rats). These studies included continued applications of 2.5% tellurium dioxide suspension, with control studies employing the identical procedure but using a nonmedicated base.

There was no indication of skin irritation or of pathological change in the animal organs, and blood smears failed to show pathological variation. It should be further noted that there were no corneal opacities in the eyes of any of the animals, and when observations were made on the eyes of

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Teles Suspension supplied by Torch Laboratories, 110 Chestnut St., Philadelphia.

From the Department of Dermatology, Temple University Medical Center, Philadelphia.

* Conducted by Wyanel Laboratories, 1355 N. Front St., Philadelphia (Study No. A 2249-T, June 5, 1953; Study No. A 5036-T, Nov. 2, 1953; Study No. A 5036A-T, Nov. 2, 1953).

rabbits, upon the instillation of 2.5% tellurium dioxide suspension and with proper control studies, there proved to be no permanent damage to the eyes.

Excretion Studies

"From the observations made on two human subjects on whose normal scalps the shampoo was employed daily on 14 consecutive days, it is evident that the absorption of tellurium through the scalp, under the conditions indicated, was insignificant. It is of some importance, moreover, in relation to the apparent thoroughness of the removal of tellurium compound from the hair and scalp by the simple procedure of washing it away with warm water, that no tellurium was found in any sample of urine.† This suggests that the subjects did not contaminate their hands with tellurium through contact with the hair in the intervals between the shampooing, for if they had done so and had ingested tellurium in this manner, it seems highly probable that a detectable quantity of tellurium would have appeared in the urine of the subjects at some time." ‡

Spectrographic determinations were made on six samples of urine before and after patients' use of 2.5% tellurium dioxide suspension as a shampoo. "Control samples run at the same time, in identical manner, to which known amounts of tellurium were added, gave distinct spectrum lines down to concentrations of 2 ppm. As no tellurium lines were obtained in any of the . . . samples we are reporting the tellurium as less than our lowest standard." §

Clinical Studies

One of us (C. S. W.) reviewed 159 case histories of patients who were using 2.5% tellurium dioxide suspension shampoo over a period of three years for the treatment of seborrhea capitis. He reported the following results: 69 cases completely controlled; 72 cases improved; 18 cases unimproved. He stated that the average frequency of application in seborrhea oleosa was 4 to 7 days and that in seborrhea sicca it was 14 to 20 days.

He was particularly impressed by the simplicity of application, since no other soap was needed prior to or after use of the tellurium shampoo. In his series there were no untoward reactions and no formation of oiliness on the scalp.

Gross observed 83 patients who were using the 2.5% tellurium dioxide suspension shampoo over a period of four years and reports that 60 were able to control their seborrhea; 10 patients were improved, and 13 were unimproved. There were no complaints of increased oiliness of the scalp (a side-effect from the use of selenium disulfide shampoo in 41% of the series reported by Bereston).[7] The tellurium shampoo produced no unfavorable reactions and was cosmetically acceptable to all patients, particularly in its ease of application as compared with other medicated shampoos employing this group of elements.

Bolus,‖ in 1954, observed 26 patients undergoing treatment with tellurium suspension for seborrhea capitis for varying periods ranging from one to six months and noted that all patients showed marked improvement and were able to control their seborrhea. He reported no unfavorable sequellae.

In January, 1954, E. W. Kieck ¶ reported on eight patients achieving excellent control of their seborrhea capitis through the use of tellurium dioxide shampoo.

Leon Goldman,# in January, 1956, briefly summarized his clinical studies of tellurium dioxide shampoo by reporting that there were no staining effect on the hair; no accentuation of scalp oiliness, as with selenium compounds, and an absence of hydrogen sulfide odor (nauseating to some patients, particularly when the shampoo is used with fairly warm water). He observed no irritation in his group of patients and considers it a good medicated shampoo.

Summary

Since it is not a sulfide, 2.5% tellurium dioxide suspension does not liberate hydrogen sulfide when mixed with hot water and is a cosmetically acceptable shampoo.

This particular milky white suspension does not stain the hair and is easily applied. Since it has been shown by laboratory excretion studies to be nontoxic, it does not necessitate additional shampooing before and after its use and is harmless, since there is no absorption of tellurium between shampoos.

Tellurium dioxide suspension does not induce the formation of scalp oiliness, nor has it produced any irritation to the skin.

† From the Kettering Laboratory in the Department of Preventive Medicine and Industrial Health, University of Cincinnati, Cincinnati.

‡ Personal communication with R. R. Suskind, M.D., and S. Barnett, M.D.

§ Submitted by Dalare Associates, Bacteriological and Chemical Research, 2300 Locust St., Philadelphia, Jan. 28, 1955.

‖ Personal communication with Michael Bolus, M.D., 618 Professional Building, Raleigh, N. C.

¶ Personal communication with E. W. Kieck, M.D., Cedar Rapids, Iowa.

Personal communication with Leon Goldman, M.D., Department of Dermatology and Syphilology, Cincinnati General Hospital, Cincinnati.

Clinical studies have shown it to be an effective medicated shampoo for the control of seborrhea capitis.

Medical Arts Building.

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Sugar Paste in the Treatment of Leg Ulcers

ADOLPH ROSTENBERG Jr., M.D., Chicago; EUGENE WASSERMANN, M.D., Dallas, Texas, and ROLAND S. MEDANSKY, M.D., Chicago

It is well known that leg ulcerations, especially those developing in association with some underlying vascular defect, can be extremely resistant to therapy, particularly if the patient is maintained as an ambulatory one. The unsatisfactory therapeutic results are attested to by the variety of such conditions. It is the purpose of this article to report our results with a useful "new" medication. Sugar paste is not original with us and has, we are informed, been used in the past for ulcers, but it is new in the sense that most dermatologists are unaware of it, and it has not, so far as we know, been written up in the dermatologic literature. The formula of the paste is powdered cane sugar, 30 gm.; wool fat (anhydrous lanolin), 60 gm., and compound benzoin tincture, 2 cc.

One of us (E. W.) first used this formula for the treatment of multiple decubitus ulcers in a patient with Parkinsonism, with excellent results. It was then decided to explore the potentialities of this medication for the healing of a variety of ulcers. We have treated 19 persons, 8 men and 11 women, whose ages ranged between 50 and 76. The diagnoses were as follows: stasis ulcers 12, trophic and/or decubitus ulcers 4, sclerodermatous ulcers 1, radiation ulcer 1, ulceration associated with mixed peripheral vascular disease 1. The average duration of the ulcers prior to sugar therapy was one year. In nine patients the ulcers healed completely. These were the four patients with trophic and/or decubitus ulcers and five of the patients with stasis ulcers. In four persons with stasis ulcer there was improvement of varying degree but not complete healing. The three persons with ulcers associated with scleroderma, radiation, and mixed peripheral vascular disease did not obtain any improvement. Three of the patients with stasis ulcers did not return for follow-up. In general, improvement was noted in one to two weeks, and in those ulcers which healed completely healing took on the average about three months. Four patients complained of some pruritus and burning in the tissue surrounding the ulcer which was of a rather mild degree and in no case necessitated interruption of the therapy. The paste was applied twice daily. The patient was instructed not to use any other medication or to apply an elastic bandage. No advice was given concerning extra bedrest or elevation of the foot. In addition to the cases included in this report, we have personal reports from several physicians who have treated other patients with the paste, with, on the whole, favorable results.

We have done no studies which would furnish any basis for understanding the mechanism by which the sugar paste works.

Summary and Conclusions

The use of sugar paste for a variety of ulcerations is recommended. While it is not contended that it will cure all or even most ulcerations, it is, in our opinion, the one most useful remedy we have employed for such conditions.

Department of Dermatology, University of Illinois College of Medicine, 840 S. Wood St. (12).

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Department of Dermatology, University of Illinois (Dr. Rostenberg and Dr. Medansky); Southwestern Medical School of The University of Texas (Dr. Wassermann).

Unilateral Keratosis Follicularis

Report of a Case Clinically Resembling Nevus Unius Lateris

WILLIAM SNYDER, M.D., Phoenix, Ariz.

Keratosis follicularis is a congenital skin disorder which begins usually in childhood and is characterized by keratotic follicular papules which later tend to become papillomatous. Sites of predilection are the head, face, extremities, chest, and inguinogenital regions. Generally, this is a symmetrical dermatosis, but unilateral involvement can occur.[1-4] The following case report illustrates this rare atypical distribution which was so striking that the clinical impression of several dermatologists who examined the patient was verrucous epidermal nevus (nevus unius lateris).

Report of Case

An 18-year-old Caucasian youth presented himself to the dermatology clinic because of a pruritic papular eruption on the right side of the trunk

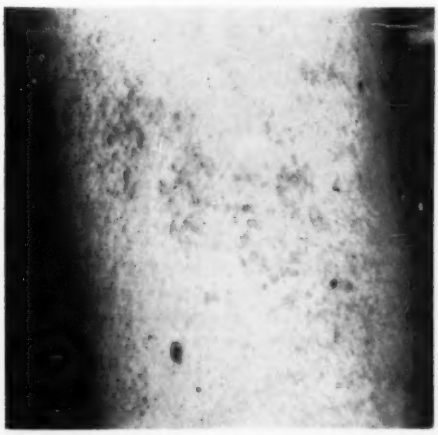

Fig. 1.—Linear group of keratotic papules on anterior right thigh. Reproduced from Kodachrome transparency.

and the right lower extremity. He stated that he had first noted clusters of small papules on the right hemithorax 14 months previously. Similar lesions appeared two and one-half weeks later on the right flank, the right thigh, and the right leg.

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From the Department of Dermatology, 3700th USAF Hospital, Lackland Air Force Base, San Antonio, Texas.

Fig. 2.—Streaked lesions of keratosis follicularis confined to right side of chest. Reproduced from Kodachrome transparency.

The only subjective complaint was itching of the involved areas. During the summer months the pruritus intensified and more papules appeared in these same sites. The past medical history revealed no significant illnesses. No cutaneous abnormalities were ever noted in the patient's family.

Examination revealed a normally developed and nourished tall blond light-complexioned youth with positive physical findings limited to the skin. On the right half of the chest anteriorly and posteriorly, the right side of the lower trunk, the anterior right thigh, and the posterior right leg there were closely agglomerated follicular keratotic papules. These had a normal flesh-to-dull-pink color. The papules were grouped in elongated ovoid patches on the thigh and leg (Fig. 1). They presented a streaked irregular configuration on the chest (Fig. 2). Some lesions approached but did not extend beyond the midline. The left side of the body was singularly free of lesions. The mucosa, scalp, nails, palms, and flexural folds were unaffected.

Although the topography of the dermatosis suggested a tardive verrucous nevus, Darier's disease was considered in the differential diagnosis because of the follicular papular morphology. A skin biopsy specimen from an involved area on the right anterior chest showed the following microscopic features (Fig. 3): The stratum corneum was moderately hyperkeratotic with some follicular plugging. The epidermis had irregular

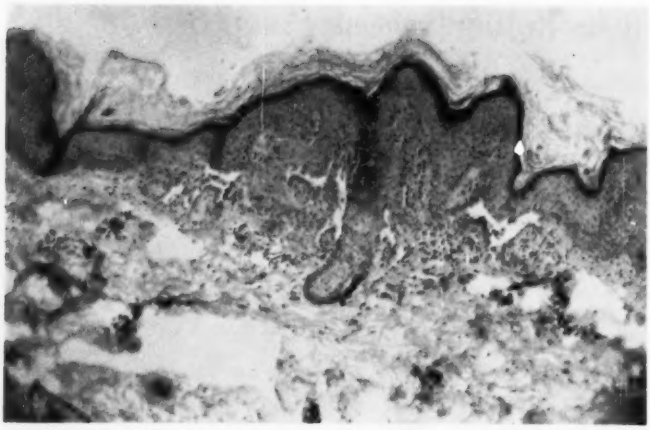

Fig. 3.—Section of skin from chest, showing corps ronds and lacunae of Darier's disease.

acanthosis and presented several individual cell dyskeratoses (corps ronds) below the granular layer. In the lower rete there was marked lacuna formation. The corium had a few scattered foci of lymphocytes. The histopathology was interpreted to be that of keratosis follicularis.*

The patient was treated with vitamin A, 200,000 units orally per day, and topical lotions and ointments containing menthol, phenol, and salicylic acid. During two months of observation there was no improvement in the dermatosis or alleviation of the pruritus. There was definite aggravation of the symptoms and severity of the eruption following inadvertent excessive sun exposure one day, the papules becoming more numerous, darker, and more hyperkeratotic. The disease maintained its unusual dextratropic localization.

Summary

A case is reported of keratosis follicularis with unilateral distribution resembling nevus unius lateris. The diagnosis of Darier's disease was confirmed by findings on biopsy.

2021 N. Central Ave.

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*E. B. Helwig, Armed Forces Institute of Pathology.

Treatment of Disseminated Coccidioidomycosis with Amphotericin B

Report of a Case

COL. RAYMOND M. WILLIAMS (MC) and CAPT. GEORGE B. SKIPWORTH (MC), U. S. Army

Amphotericin B is an antifungal antibiotic formed by a species of Streptomyces isolated from a soil sample obtained near the Orinoco River in South America. It has been shown to possess in vivo antifungal activity against experimentally induced coccidioidal infection in mice, and its action is similar to that of nystatin, in which coccidioidocidal activity has been demonstrated in vitro.[1] Although poorly absorbed from the gastrointestinal tract, amphotericin B has been shown to produce measurable blood levels when administered orally[2] and has recently been reported to be effective in the treatment of cutaneous coccidioidal granuloma when given by mouth over a period of three months.[3] Encouraging results were also obtained with the intravenous use of the drug in five stilbamidine-resistant patients having systemic North American blastomycosis.[4] The following report is of a case in which amphotericin B was administered both orally and intravenously to a patient with coccidioidal granuloma of the face known to be present from the past three years.

Report of Case

A 22-year-old Negro man lived most of his life in the San Joaquin Valley of California until entry into the Army, in June, 1955. He first observed a pustular lesion on the left cheek in 1954. The lesion was asymptomatic but was intermittently productive of a purulent discharge and was gradually increasing in size. No medical attention was required until January, 1957, when he was admitted to the Army Hospital in Landstuhl, Germany, for diagnostic studies. Findings on biospy on Jan. 24, 1957, revealed spherules of Coccidioides immitis. When he arrived at Letterman Army Hospital, in March, 1957, positive physical findings were limited to a 2.5×3 cm. granulomatous patch on the left cheek (Fig. 1) and a palpable lymph node at the angle of the left mandible. The diagnosis of coccidioidomycosis was confirmed by biopsy (Figs. 2 and 3) and culture. Further studies revealed positive coccidioidin complement fixation, 4+ in a titer of 1:128, and negative precipitin test, which were interpreted as being strongly suggestive of dissemination.[5] Skin tests with histoplasmin, coccidioidin, and PPD No. 1 were positive with 1.5, 2, and 3 cm. induration, respectively. Guinea-pig inoculation and cultures for acid-fast bacillus were negative. Hemogram, urinalysis, serology, blood urea nitrogen, liver-function studies, and roentgenograms of the chest and skeletal system were normal.

Fig. 1.—Appearance of the granulomatous patch on the left cheek prior to amphotericin B therapy.

Therapy with amphotericin B administered orally was started on April 10, 1957, with a dosage schedule of 3 gm. daily (200 mg. capsules) for a period of two weeks and 4 gm. daily for an additional four weeks. On this regimen, there was no apparent change in the clinical appearance of the lesion. The drug was tolerated well, and there were no clinical signs of toxicity. Blood, urine, liver profile, and BUN values remained within normal limits. On May 20, 1957 amphotericin B (soluble) administered intravenously was started with a dosage schedule varying from 50 mg. to 75 mg. daily or on alternate days, depending upon

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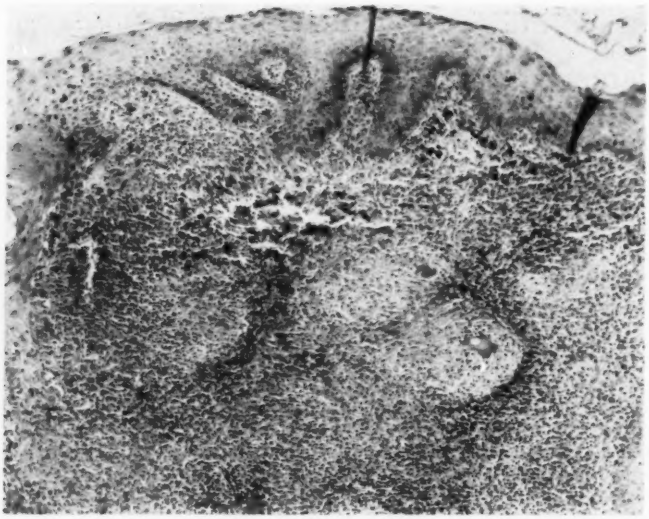

Fig. 2.—Photomicrograph of biopsy specimen taken before treatment. Hematoxylin and eosin; reduced about 15% from mag. × 100.

the patient's tolerance of the drug. It was administered in 1000 cc. of 5% dextrose solution by slow intravenous drip over a six- to eight-hour period. Treatment was terminated on June 16, 1957, after a total of 1610 mg. had been given. With the intravenous therapy, the granulomatous area became flattened and slightly reduced in diameter (Fig. 4). The drug was tolerated moderately well. However, slight to moderate temperature elevations were observed during the six-hour treatment periods, and the patient complained of anorexia, nausea, vomiting, and excessive salivation following each treatment. A weight loss of 25 lb. was observed during the course of intravenously administered therapy with amphotericin B. Laboratory studies revealed a progressive increase in the blood urea nitrogen from a pretreatment reading of 9 mg. % to a high of 40.2 mg. % at completion of therapy. Liver profile studies remained normal except for an occasional increase in the cephalin-flocculation and zinc-turbidity tests. Follow-up studies 18 days after treatment showed normal values for the hemogram, urinalysis, BUN, and liver-function tests. The coccidioidin complement-

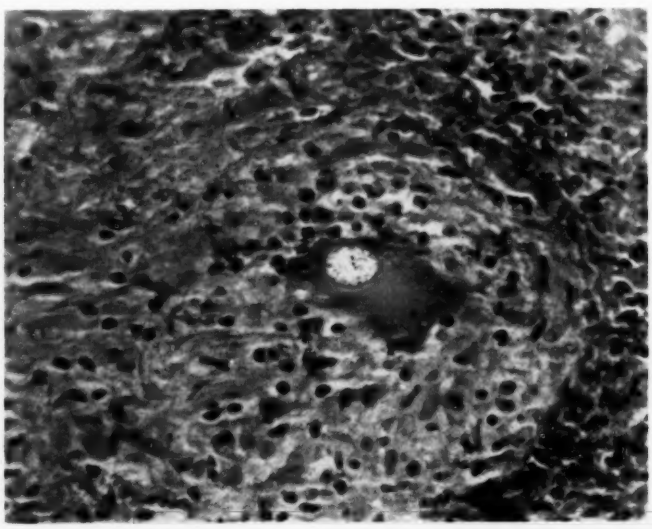

Fig. 3.—Higher magnification of Figure 2, showing typical double-refractile spherule with endospores lying within a giant cell. Hematoxylin and eosin; reduced about 15% from mag. × 500.

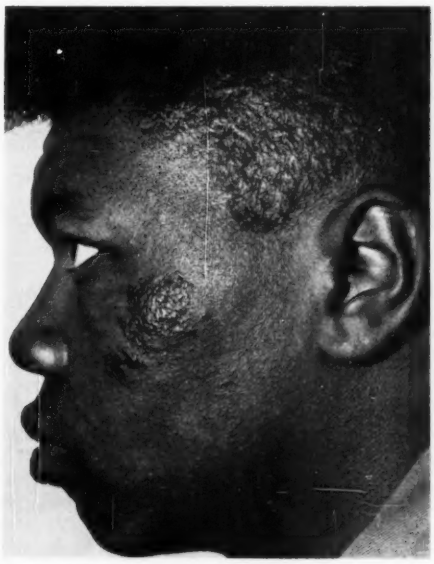

Fig. 4.—Appearance of granulomatous patch on the left cheek after amphotericin B therapy.

fixation titer had decreased from 4+ in 1:128 to 3+ in titer of 1:32. The patient was asymptomatic and was rapidly gaining weight. Findings on post-treatment biopsy remained positive in that a single spherule was found after examination of several histological sections (Figs. 5 and 6). Swab cultures from the post-treatment biopsy wound were negative.

Comment

A recent review by Winn[6] emphasized the severity of disseminated coccidioidomycosis and the absence of effective drug therapy. It was felt that this patient received definite benefit from the intravenously administered amphotericin B, but prolonged follow-up studies were not possible owing to his separation from the service. However, it is our opinion that this drug deserves further clinical trial in the treatment of disseminated coccidioidomycosis particularly with reference to optimum total dosage and duration of therapy.

Summary

Improvement was evident in a case of coccidioidal granuloma involving the face following six weeks of therapy with intravenously administered amphotericin B. Previous six-week trial, administration of the drug orally, resulted in no clinical improvement.

Amphotericin B was supplied by Dr. Galvin Hildick-Smith, Associate Medical Director, Squibb Institute for Medical Research, New Brunswick, N. J.

Serologic tests were provided by Dr. C. E. Smith, Dean of School of Public Health, University of California, Berkeley, Calif., through the support of the commission of acute respiratory diseases, Armed Forces Epidemiological Board.

Letterman Army Hospital, San Francisco.

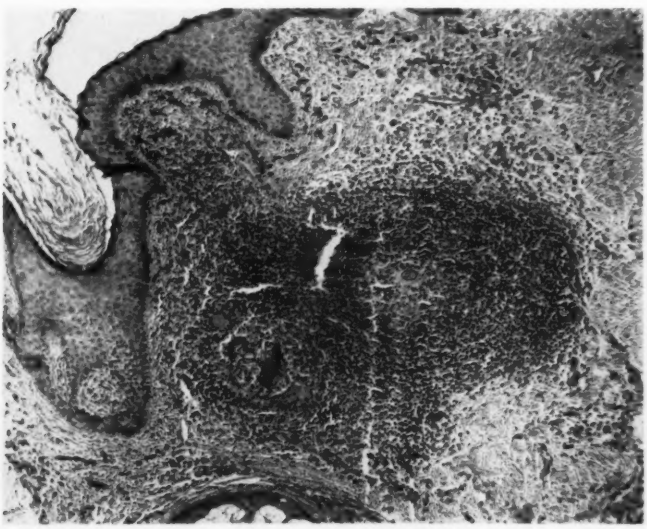

Fig. 5.—Photomicrograph of biopsy specimen taken after treatment. Hematoxylin and eosin; reduced about 15% from mag. × 100.

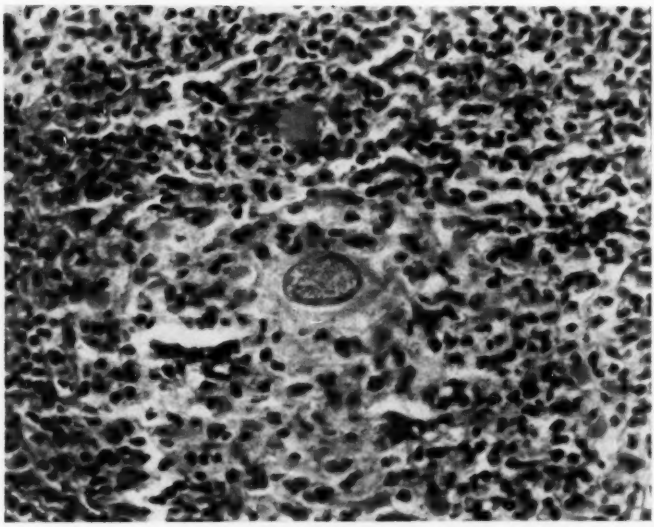

Fig. 6.—Higher magnification of Figure 5, showing a single spherule found after examination of several histological sections. Hematoxylin and eosin; reduced about 15% from mag. × 500.

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Polyethylene Squeeze Bottles for Potassium Hydroxide Solutions

HERSCHEL S. ZACKHEIM, M.D., Royal Oak, Mich.

The formation of precipitates in glass bottles containing the usual 10% potassium hydroxide solution used for examination of skin scrapings, nails, etc. for fungus elements has long been a source of annoyance to dermatologists. The precipitate consists largely of silicates due to the attack of the glass by the strong alkali solution. Upon questioning a number of practicing dermatologists it was apparent that very few were aware of the fact that polyethylene squeeze bottles now in wide commercial and laboratory use are relatively inert to the action of alkalis and that such solutions will remain clear in these bottles much longer than in glass bottles.

The accompanying photograph shows two types of squeeze bottles which are available for office use. Type A has an internal tube with a finely tapered outside point. It has the advantage of forming a very fine drop, so that there is little chance of overflooding the coverslip. Type B forms

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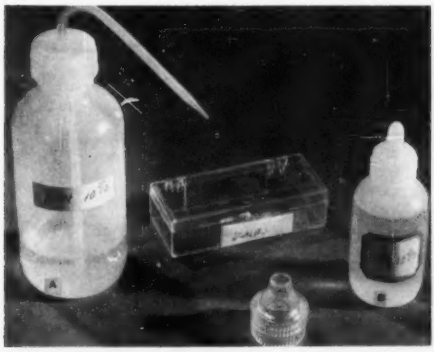
From the Department of Dermatology, Wayne State University College of Medicine (Herman Pinkus, M.D., Acting Chairman).



Polyethylene bottles and transparent plastic box.

a larger drop, but it has a protective screw cap and can be transported without leakage. These bottles in assorted shapes and sizes can be obtained from most laboratory supply houses. The Harshaw Chemical Co., Cleveland 6, publishes a particularly well-illustrated catalogue of polyethylene laboratory ware.

Of value in collecting skin scrapings, nails, hairs, etc. are the transparent plastic boxes used for packaging cortisone-ointment tubes. The knobs projecting from these boxes can be clipped or filed off so that the edge of the box rests directly against the skin. These boxes are useful when time or lack of facilities does not permit immediate examination or culture of the material. They are melted by autoclaving or boiling but can be sterilized with 70% alcohol or other cold sterilizing solutions.

114. S. Lafayette

Correction

In the article "The Use of Polyvinylpyrrolidone Iodine in Eczematoid Ringworm," by Drs. Theodore Cornbleet, Sidney Barsky, and Ben Firestein, in the March issue (p. 335), the polyvinylpyrrolidone iodine was erroneously called "Povicone." The correct name of the material used is Betadine Antiseptic, and it was supplied as such by Tailby-Nason Company, Inc., Dover, Del.

Correspondence

CONTROL OF EMOTIONAL FACTORS IN DERMATOSES

To the Editor: The statement "The skin is the largest organ of the body" recurs regularly in the periodical literature of dermatology. It appeared most recently on page 487 of the April, 1958, issue of the A. M. A. ARCHIVES OF DERMATOLOGY in the exhibit material entitled "Control of Emotional Factors in Dermatoses," by Robinson et al. It is a mistake which no amount of repetition will make true.

For what order of magnitude is the statement intended? Is it surface area? The surface area of the vascular tree is greater; the alveolar surface of the lungs is greater; the area of peritoneal surface just exceeds that of the skin. Is it weight? The musculature is weightier; the bony skeleton, panniculus adiposus, and blood are heavier. Is it volume? Again, muscle, bone, fat, and blood are more voluminous. Is it specific gravity? Bone is denser; tendon is equal in density.

One wonders why the cult of bigness and firstness invades professional thinking. Is it naïveté or is it that sort of pride for which the Greeks had a word—*hubris?*

Another curious mistake is constantly made, especially in textbooks, with regard to the weight of the skin. It is usually given as 16% (or ⅙) of the body, when it is actually 6% (1/16). Sixteen per cent would make the weight of the skin about 24 lb. instead of about 9 lb. in the "average" person of 150 lb. The figure would be 16% of the body weight, or 24 lb., if the entire panniculus adiposus were considered to be part of the skin. But we speak of the skin as consisting of epidermis, corium, and only so much subcutaneous fat (hypodermis) as envelops its deepest sweat gland and hair bulb adnexa. This, however, is not the entire curiosity. What is strangest is that books as recent as Allen's ("The Skin: A Clonicopath ɔlogic Treatise," St. Louis, The C. V. Mosby Company, 1954) and Montagna's ("The Structure and Function of Skin," New York, Academic Press, Inc., 1956) give the weight of the skin incorrectly as a percentage and correctly in kilograms. Thus, on page 2 of Montagna's book one reads: "The weight of the skin is 16% of that of the body. In man the skin weighs 4.8 kilograms, in women about 3.2 kilograms." In successive sentences it is said that the skin weighs 11.2 kg. (16% of 70 kg.) and then that it is 4.8 kg. in men and 3.2 kg. in women. Allen's book (page 1) has nearly identical sentences.

MORRIS LEIDER, M.D.
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AMERICAN BOARD OF DERMATOLOGY, INC.

To the Editor: In the April, 1958, number of the A. M. A. ARCHIVES OF DERMATOLOGY (77:438) in the special article on the American Board of Dermatology, Inc., it is reported that "Dermatologists are practicing in each state, with the exception of Wyoming." I have just learned that Dr. Everett W. Gardner is now practicing dermatology in Cheyenne, Wyo. He is thus the first dermatologist in Wyoming.

SAMUEL J. ZAKON, M.D.
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Chicago 24.

POISON IVY (RHUS) DERMATITIS

To the Editor: In the article on poison ivy (Rhus) dermatitis, by A. M. Kligman (A. M. A. ARCH. DERMAT. 77:149 [Feb.] 1958), the last conclusion (p. 177) reads as follows: "The treatment of Rhus dermatitis by the administration of Rhus allergens during the acute attack is irrational and hazardous."

This statement seems to be based mainly on the severe toxic effects encountered by Kligman, who gave intramuscular injections with enormous and heroic doses of 3-n-pentadecyl catechol (0.2 cc. of 10% solution or 20 mg.) to 11 patients having acute poison ivy dermatitis. Of these

11 patients, at least 2 had such severe reactions as to warrant hospitalization; the remainder had varying degrees of systemic and local reactions.

These data do not show that it is hazardous or even irrational to administer Rhus allergens during an attack of poison ivy dermatitis unless *high concentrations of the allergens are given.* This is one reason why we have turned from poison ivy urushiol to synthetic 3-n-pentadecyl catechol. Kligman's data demonstrate only what we have known for a long time, namely, that it is dangerous to inject highly concentrated doses of potent allergen at all times but especially during an acute attack of the dermatitis. Nor can the toxic results obtained with highly concentrated doses of 3-n-pentadecyl catechol be used to condemn the use of this compound in *dilute* doses using routes other than the intramuscular (see Keil, H.: The Prophylactic Treatment of Poison Ivy Dermatitis with 3-n-Pentadecyl Catechol Using the Wheal Method, *N. Y. J. Med.* 58:57 [Jan. 1] 1958).

The use of *highly concentrated solutions* of 3-n-pentadecyl catechol is fraught with danger when the substance is administered during the acute phase of poison ivy dermatitis or for purposes of prophylactic treatment.

H. KEIL, M.D.
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To the Editor: My only answer is that with small doses administration of allergen in *any* form, if not very hazardous, is still irrational.

A. KLIGMAN, M.D.
Duhring Laboratories
Department of Dermatology
University Hospital
University of Pennsylvania
Philadelphia 4, Pa.

Obituaries

FRANCIS EUGENE SENEAR, M.D.

1889-1958

Francis Eugene Senear, President-Elect of the International Congress of Dermatology, Professor Emeritus of the University of Illinois College of Medicine, accepted as one of the most esteemed members of his special field, died suddenly on the night of Feb. 11, 1958.

Dr. Senear was born in Salamanca, N. Y., on Nov. 5, 1889, where he attended the elementary and high school, and he later entered the University of Michigan on a combined literary and medical course. He received his Bachelor of Science degree and his medical degree at the conclusion of his medical course, in 1914. He became a member of the Nu Sigma Nu fraternity at the University of Michigan and during his last year served as fraternity president. He also held membership in Alpha Omega Alpha and Sigma Xi. From 1914 to 1915 he was an intern at the University Hospital, and he became Instructor in Dermatology and Syphilology from 1915 to 1916. At the termination of his service, he became assistant to Dr. William Allen Pusey in Chicago and at the same time became an instructor at the University of Illinois College of Medicine. He remained with Dr. Pusey from 1916 until 1926, at which time he opened his own office. He graduated from the instructorship in dermatology to the assistant professorship and finally became Professor of Dermatology and Syphilology at the University of Illinois College of Medicine. This position he held until 1955, when he became Professor Emeritus.

FRANCIS EUGENE SENEAR, M.D.
1889-1958

Dr. Senear was married in 1917 to Anne E. Seitz. Mrs. Senear died suddenly in New Orleans while he and she were preparing to embark on a trip through the Evangeline country.

He is survived by one son, Allen Eugene Senear, his wife, and their four children, of Seattle.

During his active life in Chicago, Dr. Senear had, in addition to his teaching and investigative pursuits, several other activities in connection with his profession. He was consulting dermatologist to the Illinois Central Railroad and to the Research and Educational Hospitals, University of Illinois, to St. Joseph Hospital, and to the Presbyterian Hospital, of Chicago. He was secretary of the Section on Dermatology of the American Medical Association from 1930 to 1932 and was its chairman in 1933. He was a member of the Chicago Dermatological Society and served as its president in 1927 and 1928. He was a member of the American Dermatological Association and became its president in 1939. He was President of the Section on Dermatology of the Pan American Medical Congress in 1935, President of the American Board of Dermatology and Syphilology from 1946 to 1949, President of the American Academy of Dermatology and Syphilology in 1950, Honorary Vice-President of the International Congress of Dermatology in London in 1952. He was an honorary member of the Australian, Italian, and Manhattan dermatological societies and of the British Association of Dermatology. He was a corresponding member of the Danish, Swedish, French, and Austrian dermatological societies. Between the years of 1922 and 1930 he was editor of the "Year Book of Dermatology."

In 1939, Dr. Senear's alma mater, the University of Michigan, conferred upon him an honorary degree of Master of Science. In addition to these many activities, Dr. Senear made many contributions to his special field. Together with his assistant, Dr. Barney Usher, he made a noteworthy contribution in which he differentiated true pemphigus from the exfoliative type, which now is known in the literature as the Senear-Usher syndrome.

At the conclusion of his active service at the University of Illinois and on the occasion of his achieving emeritus professorship his many former students and co-workers, of whom there were more than one hundred, including wives, celebrated the occasion by a testimonial dinner.

With all these activities one would have imagined Dr. Senear to have been a man harassed by these many duties and obligations. Quite the contrary, he had a serene quiet manner and never seemed to be the least bit hurried, and over the years few, if any, found him frustrated, angry, or impatient.

He lived in a very large home in Winnetka, Ill., and had a most delightful hobby which made him ultimately a connoisseur of English china and Georgian silver. His entire home was filled with treasures, and he seemed to know the value of each piece of his collection.

From the standpoint of recreation, he made many trips to various parts of Europe and to the Hawaiian Islands, and he kept up his attendance at medical meetings almost without absenteeism. His last European trip included his presence at the International Congress of Dermatology in Stockholm in 1957. It was at this meeting that he was chosen President-elect of the forthcoming congress to be held in the United States in 1962. This would seem to have been the greatest honor that could have been conferred upon him. Dr. Senear had one other outlet for his many activities. After Mrs. Senear's death, he became very active in the

local Episcopal Church, and during the past several years he was one of the vestrymen of the congregation.

Fran Senear is gone. His many contributions to his special field of medicine will perpetuate his name in medical history. His sincere and gracious personality will linger with his colleagues, his students and especially with his many close friends as a delightful memory.

Udo J. Wile
Ann Arbor, Mich.

International Tribute to Francis Eugene Senear, M.D.

On August 5, 1958, in Stockholm, Sweden, the delegates to the Assembly of the International League of Dermatologic Societies unanimously approved the recommendation of their International and Executive Committee and elected Francis Eugene Senear to be President of the Twelfth International Congress of Dermatology.

Senear was selected because he was of unquestioned stature, not only in his own country but throughout the world. He was selected because he was modest but not timid; a leader, but not a dictator; a liberal but not spineless; a physician selflessly dedicated to dermatology and devoted throughout his life to the welfare of all those within its ranks, and above all because he was not only respected but universally trusted and beloved.

The news of Dr. Senear's sudden death on February 11, 1958, came as a sad shock to dermatologists everywhere. As representatives of international dermatology, we speak for members of our confraternity in every land in expressing our sense of grievous loss and in paying the final tribute of affection and respect to Francis Eugene Senear, late President of the Twelfth International Congress of Dermatology.

The Executive Committee of the
International League of
Dermatological Societies
and
The International Dermatologic Committee

Marion B. Sulzberger, President	The United States
Sven Hellerstrom, Secretary General and Treasurer	Sweden
L. A. Brunsting	The United States
R. Degos	France
F. Flarer	Italy
J. Gay-Prieto	Spain
W. Jadassohn	Switzerland
F. Kogoj	Yugoslavia
S. Lapière	Belgium
A. Marchionini	Germany
G. B. Mitchell-Heggs	Great Britain
M. I. Quiroga	Argentina
C. H. Flodén	Sweden (ex officio)
D. M. Pillsbury	The United States (ex officio)
E. D. Osborne	The United States (ex officio)

On Francis Senear's Selection As President of the Twelfth International Congress of Dermatology *

I am grateful to the President and his committee for the privilege of saying a few laudatory words about the selection of our Francis Senear as President of the Twelfth International Congress of Dermatology, which will be held in the United States, in 1962.

The first International Congress was held in Paris, in 1889. This was followed in order by congresses in Vienna, London, Paris, Berlin, New York, Rome, Copenhagen, Budapest, London, Stockholm, and now again in the United States, fifty-five years after the first American meeting.

Dermatology has changed a great deal since 1907, and Dr. Senear has seen and been responsible for many of these changes and advances. His name will now be enrolled with the former presidents. I should like to mention the names of these renowned dermatologists so that you may appreciate in what distinguished company Dr. Senear's name will be included.

A. Hardy, the great French dermatologist, who established the first course in dermatology in Paris, in 1862, presided at the first congress, held in Paris, in 1889.

Moritz Kaposi, the successor of Hebra, was in the chair at Vienna, in 1892, where the problem of the identity of lichen ruber acuminatus or pityriasis rubra pilaris was the subject of the principal debate.

Sir Jonathan Hutchinson, that versatile surgeon, oculist, and dermatologist, led with distinction in London, in 1896, and I believe it was then that Boeck and Hutchinson agreed on the unity of Hutchinson-Boeck's generalized sarcoidosis.

Ernst Besnier, whom Jadassohn told me was the man who most inspired him, headed the second Paris meeting, in 1900. His name is best remembered because of his identification of lupus pernio. This was at the time of the Paris exposition.

Edmund Lesser, who was one of the first professors of dermatology in Germany, was president in 1904 at the Fifth International Congress, held in Berlin, where tuberculosis of the skin, because of Koch's discovery, received much attention.

James C. White was the presiding officer at the Sixth International Congress, held in New York in 1907. He was one of the founders of the American Dermatological Association, a pupil of Hebra, and we think of him because of the introduction of crude coal tar for the treatment of eczema.

T. De Amicis was president in Rome in 1912. His name is not so well known by us, but he did much work on lupus vulgaris.

C. Rasch headed the postwar congress in Copenhagen, in 1930, where the dissertations were more along the line of present-day meetings. Eczema, syphilis, allergy, etc., were main themes, and such leaders as Jadassohn and Darier awed the audiences with their learned and exhaustive treatises on eczema. This, incidentally, was the first congress in which American participation was notable. Dr. Pusey was on the panel on eczema.

Ludwig Nekam, with the help of our own Stephen Rothman, made the ninth meeting, held in Budapest in 1935, a notable one. Many Americans attended, and, to me, the most interesting papers were Jadassohn's, Darier's, Little's, and Pol-

* Read at the Meeting of Chicago Dermatological Society, Jan. 15, 1958. Dr. Senear was present.

litzer's reviews of their fifty years in dermatology. These four papers should be read by all. They are personal and, one might say, official, historical records of the growth and progress of Teutonic, French, English, and American dermatology as seen through the eyes of those four immortal leaders.

The second London congress, held in 1952, led by Sir Archibald Gray, is so recent that most of you are familiar with its proceedings. Here, American dermatology came into its own. Drs. Brunsting, Pillsbury, Sulzberger, and many others demonstrated the commanding position of our progress, and they talked with the authority of experience on eczema and the steroids.

The Stockholm meeting, held in 1957, is fresh in your minds. Guido Miescher, who is Bloch's successor and who now holds a very special position in international dermatology, was the president. Physiology of the skin, bullous dermatoses, the reticuloses, and many other topics demonstrated the present trend of dermatologic thinking. Classification and morphology had had their day. The relation of the skin to the bodily economy was the concern of the leaders at this Eleventh Congress, while isolated but important observations were given space and consideration to the extent that dermatologists knew that they still had a special place in medicine and had not been engulfed by its more inclusive branches. It was reassuring, too, to note that, although we were giving more profound consideration to the pathogenesis of the diseases that we encountered, we still maintained our unique and refined inspectional approach.

The proceedings of the International Congresses are indeed the history of dermatology, and the names of the officers and participants represent the leaders of the times.

The selection of Dr. Senear as president of the Twelfth International Congress is not only a well-deserved personal tribute, but it is also a distinct acknowledgement of the position of Midwest dermatology in our country.

Dr. Senear represents the acme of accomplishment in practical clinical dermatology. His leadership comes primarily because of his thorough knowledge of skin diseases such as we see and treat and think about every day. It is no small task to become familiar with all of the facets of these many conditions. Day-to-day observation of patients teaches one to respect the natural history of the diseases that one is dealing with, and constant surveillance of international literature keeps one aware of changes in thinking and of new findings. Dr. Senear has done just that, and his keen scrutiny, his decisions based on thorough knowledge, and his respect for facts have kept him the level-headed clinician that he is.

His personal integrity, his lack of prejudice, his kindly consideration, and his day-to-day living have added to his professional accomplishments to that degree that his choice as President of the Twelfth International Congress was a crowning reward for a dermatological life well lived.

We congratulate him, we shall work with him, and we shall aid him in every way to make the second American congress a success.

H. E. Michelson, M.D.
Minneapolis

Eulogy Read at the Meeting of the Chicago Dermatological Society, Feb. 19, 1958

On Feb. 11, 1958, the Chicago Dermatological Society lost one of its most distinguished and beloved members, Dr. Francis Eugene Senear. . . . Although

he was only 68 years old at the time of his death, Dr. Senear's service to the Chicago Dermatological Society and to American dermatology spanned many years. After receiving his M.D. degree from the University of Michigan in 1914 and obtaining his dermatological training there, Dr. Senear came to the University of Illinois, in 1916, and there began a long and distinguished career that brought great luster to the University and in addition had a profound influence on the practice of dermatology in Chicago. The Chicago Dermatological Society is a towering edifice shaped by the men and women who compose its membership. In his quiet and unobtrusive way Dr. Senear throughout his long period of active membership contributed greatly to the strength and prestige of our Society, and he did much to advance the standards of our specialty.

As head of the Department of Dermatology at the University of Illinois for 32 years Dr. Senear earned for himself and for his department universal respect and the dignity of being utilized as a major factor in the education of medical students. He was an inspiring and dedicated teacher, and for his students he provided the spark of inspiration that attracted many of them to his specialty. To them and to the countless others who had the good fortune to meet with him here and at other dermatological gatherings he constantly served as an example of honesty, integrity, and dedicated service to the sick.

Dr. Senear was blessed with an orderly mind. His many contributions to dermatologic literature and his countless lectures to medical groups in many countries did much to marshal the facts in many confused areas of dermatologic knowledge and to leave them in an orderly and logical arrangement. It is to be regretted that the burden of his many activities did not permit him the time to write a textbook, but his many lucid expository papers had a great influence on the writing of textbooks by other authors.

Dr. Senear was a modest and unassuming man, and he had the humility of greatness. Nevertheless, in each group of which he was a member the mantle of leadership came to him naturally and without questions. . . . It is a tribute to the unique love and admiration that he inspired that, in his advance to the top in all our local, national, and international societies, Dr. Senear did not arouse any trace of envy. In all the years that I knew him I cannot recall ever having heard one unkind remark about him from anyone.

In his very orderly fashion Dr. Senear had set a timetable for himself, which he did his best to keep. He retired from active work at the University of Illinois at 65, as he had planned. His next aim was to retire from private practice at 70 and then to spend his leisure time in travel, which he loved so much, and in writing a textbook on dermatology. Dr. Senear was a very religious man, and I am sure that he would not have questioned the timing of his abrupt and final change of plans. Dr. Senear has retired now and we must relinquish him to the world of memories. These memories are all pleasant, for we can remember him only as a good man, a good friend, and an inspiring teacher.

Most eulogies conclude with sorrow and sadness. That of Dr. Senear, however, must ascend to a note of exaltation. We are grateful for our good fortune that for so many years our lives were illuminated and enriched by a close friendship and collaboration with one of the giants in the history of dermatology. We rejoice also that Dr. Senear was spared the agony of witnessing the gradual

deterioration of his own eventual senescence and that he retained good health, both physical and mental, until the very moment of his death.

MARCUS R. CARO, M.D.
Professor of Dermatology and
Head of the Department
University of Illinois
College of Medicine
Chicago

. . . . My friendship with Fran began many years ago. He was the upper classman who pledged me to a medical fraternity. From that time on, beginning with a year with him on Dr. Wile's service and frequent visits during his early years with Dr. Pusey in Chicago and continuing on down through the years, whenever the opportunity presented, we spent time together. It was the kind of friendship that recognizes no hiatus; at each meeting we just carried on as though we had seen each other the week before.

On so many occasions I needed, and had, his advice, like that of an older brother, and he was always "right." To my mind, his qualities were of the kind that are "born in" the person, not "acquired." Certainly, I deem myself among the more fortunate to have had the friendship of this modest, kindly, and most accomplished gentleman over a period of forty-odd years. Life's span provides few friendships of this kind, and all can appreciate my feelings in this loss.

LYLE B. KINGERY
Portland, Ore.

The passing of Fran Senear has been a deep personal loss. His relationship to me has been that of teacher and friend. It was in the office of Dr. W. A. Pusey, in 1926, where at that time he was Dr. Pusey's associate, that I first met him. He took me under his personal wing and rapidly passed on to me his intense absorption in dermatology. His interests were primarily clinical, his writings clearly demonstrating his capacities in that field. He belonged to the school that believed a study of descriptive dermatology was of paramount importance. His examination of a dermatosis was a treat to behold; his capacity as a teacher, of the highest order.

It was my good fortune to work with him on our original case of pemphigus erythematodes. It was here that he demonstrated his powers of observation, his attention to detail, and his ability to correlate his findings. Since the original description little has been added and general interest has been maintained.

His interest in Canadian dermatology and his kindness to my Canadian colleagues have been deeply appreciated. We will miss him.

BARNEY USHER, M.D.
Montreal, Canada

The New, Newer, and Newest

The International Committee of Dermatology has elected Don Pillsbury to be President of the XII International Congress of Dermatology, to fill the vacancy left by the sad death of Dr. Francis Senear. A Pillsbury-Osborne-Sulzberger team should assure a very successful Congress.

It has been said that the time to move to Southern California is when you have reached the metallic age, with silver in your hair, gold in your teeth, and lead in your pants. The salubrious weather is supposed to be conductive to *laissez faire*. If so, it was not evident, for dermatology in the area is as active as can be. Just yesterday I attended a meeting of the Los Angeles Dermatological Society which was well-attended, spirited, and informative. It was a young man's meeting, and the open character of the discussions reflected it—even old friends from Chicago, now settled out there, seem to have come to the fountain of youth. As at other meetings, some of the discussions, though excellent to hear, were unfortunately of a sort that do not lend themselves to the printed page.

Tom Sternberg's department at U. C. L. A. is a dream. He has an active, hardworking, full-time staff of dedicated men, a large voluntary staff, a comfortable patient-load, an adequate budget, full cooperation from administrative offices, and good rapport with all other departments. But, as in other institutions, dermatology still is something of a step-child, for his is a department in the division of medicine and it is quartered in a corner of the basement. Even so, the appointments are such that it is referred to as the "country club" department.

Sternberg and Paul Le Van, on Sept. 7, will be in Tokyo to speak on mycotic diseases for the Fifth International Congress on Diseases of the Chest.

In sunny California, one office that we visited had an ultraviolet lamp in each of the treatment rooms, and in a swank residential suburb the health officer reported 90 cases of head-lice among school children.

In Kansas City, Justin L. Mooney was elected President of the Kansas City Dermatological Society; Edwin Pfuetze, Vice-President, and Normal Asel, Secretary. In New York, Morris Leider is now President of the Bronx Dermatological Society and Henry Silver is Secretary.

Louie Brunsting and Ham Montgomery were elected honorary members of the British Association of Dermatology and also of the Venezuelan Society of Dermatology; Clarence Livingood, Don Pillsbury, and I were elected corresponding members of the Argentine Association of Dermatology and Syphilis.

The conference on psoriasis, conducted by the New York Academy of Sciences, May 9, 1958, was chairmanned by Carl Nelson and addressed, among others, by George Hambrick Jr., Philadelphia; Elson Helwig, Washington, D. C.; Otto Braun, Falco, Germany; Daphne Roe, Poughkeepsie, N. Y.; Peter Flesch, Philadelphia; Allan Lorincz, Chicago; Simon Rothberg, Bethesda, Md.; Alfred Bollet, Detroit; Harris Samitz, Philadelphia, and Jacob Bleiberg and Sydney Clyman, New York.

Not all persons are so enamored with psoriasis, however. Aloise Heath, in the Jan. 4, 1958, *National Review*, in a critique of movie magazines remarks: "It is hardly surprising, of course, that readers of movie magazines need charm and want Elvis Presley. What is surprising, to this laywoman at any rate, is the fact that, according to the advertising columns, at least 95 per cent of these readers seem to suffer from the same exotic illness. For most of these periodicals advertise no less than fifteen remedies for a strange and horrible disease called psoriasis. I don't know what psoriasis is, and I don't intend to look it up because it sounds like the kind of thing I should like to continue to not know about. It is obviously strange and horrible, however—otherwise it would not be called psoriasis; it would be called chicken-pox, or backache—and I feel that the fact that this malady is suffered by a great majority of thirty or forty million Americans all of whom read movie magazines, is significant enough to demand an immediate and intensive investigation by persons other than myself, who am too busy."

In the mail: "I have a son who for eleven months, because of his Christian integrity has been confined to a Federal prison camp. . . . He . . . scalp condition. . . ."

H. R.

Society Transactions

NEW ENGLAND DERMATOLOGICAL SOCIETY

Maurice M. Tolman, M.D., President
Paul J. Catinella, M.D., Secretary
Oct. 9, 1957

Case for Diagnosis: Annular Sarcoidosis; Necrobiosis Lipoidica Diabeticorum sine Diabeta? Presented by DR. F. RONCHESE.

A stenographer aged 41 was previously presented before this society on Dec. 1, 1948, and on April 12, 1950, with the diagnostic possibilities of lupus erythematosus, necrobiosis lipoidica diabeticorum, tuberculosis of undetermined type, and sarcoidosis. Biopsy showed granuloma.

About 10 years ago lesions consistent with those of cutaneous sarcoidosis developed on the scalp, the back, and the abdomen. They cleared up gradually, and only scars are visible at present. Clearing was attributed to cortisone therapy.

There are now oval-ringed erythematous lesions on the legs only. The borders are reddish, raised, and firm. The central area is smooth, shiny, somewhat scarred, and telangiectatic. Some central areas present normal skin. On the left leg are seen areas which have spontaneously returned to normal.

Urinalysis and examinations of the blood were normal.

Biopsy, Oct. 9, 1957: "These sections of skin contain a granulomatous process in the dermis. The overlying epidermis is not particularly remarkable. Dermal appendages are absent except for an occasional eccrine sweat gland and duct. Throughout the dermis in relatively large foci are areas where the collagen stains more deeply and more homogeneously than elsewhere and in a rare focus seems to be frankly necrotic. Surrounding these foci are zones containing relatively dense infiltrates of lymphocytes and mononuclear cells, probably histiocytes. An occasional focus reveals a multinucleated giant cell of the Langhans type. No definite tubercle formation is identifiable. Rarely the large giant cells contain a vacuole. One small focus of subcutaneous fat is seen into which the infiltrate extends.

"Sudan 4 and Sudan Black B stains revealed only a rare focus containing minimal amounts of sudanophilic material at the edge of one of the necrobiotic zones. PAS stain failed to reveal staining of the necrobiotic zone although the epidermis stained normally. No fungi were identified. The acid-fast stain was negative.

"This is a granuloma containing zones of altered collagen staining. Granuloma annulare cannot be excluded and necrobiosis lipoidica must be seriously considered. Neither of these characteristics give the clinical picture described in this patient, but could be atypical forms of this disease. The lack of tuberculoid structure would tend to make sarcoidosis, tuberculosis and leprosy unlikely, although they cannot be eliminated on histologic grounds alone" (Herbert Mescon, M.D.).

Discussion

DR. FRANCESCO RONCHESE: The findings on biopsy in 1948 from the lesions on the back, now healed with good scars, were submitted to several dermatopathologists, and the consensus was that the entity was some form of sarcoidosis. The present leg lesions, of 10 years' duration, resemble necrobiosis lipoidica, and this diagnosis is supported by the pathology. Against necrobiosis is the fact that the lesions in several areas involuted spontaneously. It would be peculiar if this patient had necrobiosis lipoidica instead of sarcoidosis 10 years ago.

DR. E. MYLES STANDISH: Clinically, from a distance, one's first impression is of pronounced necrobiosis lipoidica, but on closer examination one finds that the color zones of the lesion are reversed. Instead of a bluish erythematous margin there is a raised indurated yellowish margin with the bluish portion on the interior edge of the advancing lesion. Then, although there is atrophy, the central portion of the lesion does not have that yellowish lardaceous appearance shown by most of the necrobioses. I should think, with the history of prior lesions on the body which involuted, leaving scars, plus the biopsy findings, that we must consider this as having been the same entity all along—that is, sarcoidosis.

Case for Diagnosis. Epidermoid Carcinoma; Keratoacanthoma (Tumor-like Keratosis of Poth Type)? Presented by DR. HARVEY B. ANSELL.

A white woman aged 44, a school teacher, is presented with an eruption of the right thumb of

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one month's duration. The patient has had "warts" scattered about her body for as long as she can remember. They have been present about the ear canals since about the age of 20. In 1955 she developed a large wart about the nail of the left middle toe which was amputated because the "wart interfered with walking."

Early in August, 1957, the patient accidentally burned her right thumb over the dorsum of the metacarpophalangeal joint. She developed a warty growth at the site of the burn, and three weeks after its occurrence the growth was excised by a surgeon. The pathologic report was epidermoid carcinoma, and, because of this, a wart which had been present just above the left ankle since March, 1957, was excised. Immediately following excision of the growth of the thumb, marked swelling and vesiculation of the dorsum of the thumb developed. The patient stated that she was sensitive to Novocain, which had been used for anesthesia, but she had failed to notify the surgeon of this. As the vesicles on the thumb healed she developed many new warty growths.

There is a nontender, firm, erythematous, slightly elevated, verrucous eruption involving the entire dorsum of the proximal phalanx of the right thumb. Warty papules are scattered about the external ear canals.

A VDRL slide test was negative.

Findings on three biopsies were reported as epidermoid carcinoma.

Discussion

DR. LEON BABALIAN: I understand that since 1953 this patient has developed on the upper and lower limbs several lesions with the same characteristics, all labeled squamous-cell carcinoma, and which Dr. Ansell considers to be keratoacanthoma. Taking into account the clinical and pathologic data, I wonder if this is not what Ferguson Smith was the first to describe as multiple primary self-healing squamous epithelioma of the skin (*Brit. J. Dermat.* 46:267, 1934). In spite of its pathology it is not a true squamous-cell carcinoma, as it never metastasizes. It is just an "epitheliomatiform reaction," according to Gougerot (*Bull. Soc. franç. dermat. et syph.* 9:1737 [Dec. 12] 1935). I also feel that although keratoacanthoma and Ferguson Smith's disease both develop on inflammatory lesions, they are two different conditions, for the following reasons: (1) Keratoacanthoma has a few weeks' duration and seems to confer an immunity, whereas Ferguson Smith's disease is lingering, with formation of new lesions over a period of years, each of months' duration; (2) self-healing is constant in keratoacanthoma and inconstant in Ferguson Smith's disease (Charteris, quoted by Sommerville, *Brit. J. Dermat.* 62:488, 1950); (3) in keratoacanthoma there is formation of a tremendous core of cornification, while in Ferguson Smith's disease the keratinization does not exceed the formation of a common horn pearl.

For all these reasons, I feel that this case represents just an epitheliomatiform reaction of the Ferguson Smith type which developed on infected cutaneous lesions.

DR. HARVEY B. ANSELL: The lesion is different today than it was when I first saw the patient in consultation, 11 days ago, in that the central portion of the tumor has undergone involution.

DR. MAURAY J. TYE: Whenever she cuts her hand, except on the palm, the patient develops this type of warty growth.

DR. HERBERT MESCON: She had a lesion on the leg, too. In the last few years the entity of keratoacanthoma has become more widely known, and some of the pathologists of late tend to diagnose this disease rather frequently as compared with the diagnosis of more conservative pathologists on the same lesion. Unless one has a typical clinical and histologic picture, the disease must be treated as a malignant lesion.

The one complete lesion that has been excised here has most of the accepted criteria for making a diagnosis of keratoacanthoma histologically, and it fits in clinically.

Only half the biopsy section of the other lesion was presented, and, if the other half corresponded with it, this, too, fitted in with keratoacanthoma. Ten years ago these would both have been diagnosed histologically by competent pathologists as squamous-cell carcinoma, and so when we go through the literature and find cures of epidermoid carcinoma we must take into account the possibility that many of them may have been keratoacanthomas.

DR. HARVEY B. ANSELL: In 1939 Poth reported a case (Poth, D. O.: Tumor-like Keratoses: Report of a Case, *Arch. Dermat. & Syph.* 39:228 [Feb.] 1939) in which the patient sustained a severe sunburn on the dorsa of his hands and subsequently developed keratotic tumors in the burned areas. Sections were submitted to five pathologists, and the diagnoses were as follows: verruca vulgaris, hyperkeratosis, carcinoma (2), and tumor-like keratoses. All the lesions underwent spontaneous involution. Poth's patient also had had verrucae on the dorsa of the hands.

The patient presented today developed vesiculation following a burn from an old-fashioned wooden match instead of from sunburn, as did Poth's patient. Within three weeks she developed a tumor that was excised and reported as epidermoid carcinoma. She again developed vesiculation and again a tumor developed in that area. During the past 11 days the tumor has begun to involute spontaneously.

Since self-healing tumors have been described under a variety of names, including Ferguson Smith epitheliomata and molluscum sebaceum, I followed the suggestion of Ereaux (Ereaux, L. P.; Schopflocher, P., and Fournier, C. J.: Keratoacanthoma, A. M. A. Arch. Dermat. 71:73 [Jan.] 1955) and presented this case as one of possible keratoacanthoma, but because of the similarity to Poth's case, I added his name.

The question is what to do with this patient. I am tempted to do nothing, but if involution is not complete within the next two weeks I hope to obtain another biopsy specimen.

Note: Biopsy of the residual nodule on Oct. 25 was diagnosed as keratoacanthoma.

Tumor Stage of Melanotic Freckle (Hutchinson). Presented by Dr. Herbert Mescon.

A white woman aged 65 is presented from the Massachusetts Memorial Hospitals with a lesion in the right temporal region which has been present for 20 years. About 1937 the patient noted a small flat pigmented area on the right temporal region which grew very slowly during the next 15 years. In 1952 she noticed an elevated asymptomatic growth on the upper border of this lesion, and another was noted on the lower border in 1955. These reached the size of split peas. Since April, 1957, the patient has noted slight bleeding on these elevated areas on combing the hair, with low-grade itching. There have been no pain and no scab.

There is an ovoid macular area of pigmentation on the right temporal region 2.3 by 1.4 cm. in size. The pigmentation is not dark nor is it uniform, and there is a tendency toward clearing near the center. There are two papules. One is at the upper border, 0.3 cm. in diameter and elevated 0.2 cm., slightly keratotic, and the color of normal skin. It has no ulcerations and no crusts. The other is at the lower border, 0.4 cm. in diameter and elevated 0.2 cm., and is of similar nature. There are no palpable preauricular, submaxillary, or cervical glands.

Findings on biopsy of the nodular area showed malignant melanoma. Findings on biopsy of the flat area showed a junction nevus with activity.

It is planned to excise the lesion widely, with removal of the underlying fascia and muscles but without dissection of lymph nodes in the preauricular or submaxillary areas.

Discussion

Dr. Herbert Mescon: This case again emphasizes the fact that you can have "malignant melanomas" that do not act as such. The question is, how are you going to recognize a Hutchinson freckle before it goes into the nodular stage so that you can do something about it?

Dr. Bernard Appel: I think that in any case where this is suspected the lesions should be excised by the knife and the answer given by the pathologist.

Dr. Francesco Ronchese: Suppose the pathologist found malignant melanoma. What would you do?

Dr. Bernard Appel: Whatever is done, the end-result will probably be the same.

Dr. Herbert Mescon: My question is what to do before it shows nodules. Then it is probably going to be a malignant melanoma, whatever that means. Before it shows nodules, when you have just the freckle as a pigmented irregular spot, how do you distinguish it from other freckles, and, if you can distinguish it, what do you do about it before it shows elevation?

Dr. Alfred Hollander: I believe that one cannot differentiate the melanotic freckle from any pigmentation of long standing until the pigmentation shows a change in color and appears darker. Then or later there will be slight elevation and possibly scaling. As soon as these changes occur a biopsy should be performed, and, if necessary, adequate excision should be carried out. If the melanotic freckle does not show any change over the years it should be left untreated.

Dysproteinemic Purpura of the Hypergammaglobulinemic Type (Purpura Hyperglobulinemia of Waldenström). Presented by Dr. Leo Blacklow.

A woman aged 60 developed pruritic papules on the legs four years ago, followed by involvement of the arms. Pigmentation has followed these lesions.

For many years the patient has had a tendency to bleed easily. Five years ago she underwent surgery at the Baker Memorial Hospital, and at that time the bleeding and coagulation times were normal. A consulting hematologist was unable to establish any defect in bleeding or clotting. The patient is a diabetic and has elevated blood pressure.

The early lesions are 2 to 3 mm. in diameter and consist of urticarial papules mixed with petechiae and telangiectases. Hyperpigmentation, depigmentation, excoriation, and scarring are present.

Hematologic studies revealed increased γ-globulin values.

No treatment has been given.

Discussion

Dr. Walter F. Lever: I think that this is an example of chronic purpura. In the old days these cases were described under various names, such as Majocchi's disease, Schamberg's disease, and Gougerot-Blum's disease. Nowadays there is

a tendency to put them all together, since there are too many in-between varieties among these so-called entities, and the term that may be used is progressive pigmented purpura.

Any inflammatory purpura, as this case, is apt to develop over the months and years an increase in the amount of γ-globulin in the serum, because, since it is an inflammatory disease, there is a production of nonspecific antibodies. I question very much whether we have to attach the special name of hyperglobulinemic purpura of Waldenström to this case. The cases described by Waldenström had cryoglobulins in the serum, and even that is probably merely evidence of the allergic state of which the purpura is the main clinical manifestation.

DR. AARON B. LERNER: I should like to know more about the serum proteins of this patient. Is the cryoglobulin a γ-globulin, as most of them are? Most patients with cryoglobulinemia have multiple myeloma or leukemia. However, on occasion they have only hyperglobulinemia without any other apparent abnormality. Waldenström has described purpura associated with cryoglobulinemia and also with other forms of hyperglobulinemia. He divided his cases into those with globulins of ordinary solubility and those with hairy cryoglobulins.

Colloid Degeneration (Colloid Milium) of the Skin. Presented by DR. LESTER BIENVENU and DR. WALTER F. LEVER.

A white man aged 35, who drives an oil truck, is presented from the Massachusetts General Hospital with an eruption on the backs of the hands, sides of the neck, and cheeks, of three or four years' duration. The eruption appeared on the left hand, at the beginning, and on the right hand about six months or so later, going on to involve the other areas. It is asymptomatic.

There are multiple small, brownish, flat-topped and umbilicated papules on the dorsa of the hands. The lesions are rather closely set, with some confluence on the right hand. A few lesions are noted on the sides of the neck, upper part of the cheeks, and left side of the forehead.

Biopsies were made from the hand, neck, and cheeks. A hematoxylin and eosin stain on the specimen from the hand showed an atrophic epidermis. The dermis was very thin and tenuous. Beneath the dermis was a discrete space filled with a homogenized eosinophilic material containing only a few nuclei, with fissuring and "falling out" of the material. Just below the level of the epidermal pegs the dermis became normal. There was no adjacent inflammatory infiltrate. Congo red and toluidine stains ruled out the presence of amyloid.

Because of the presence of lesions in sun-exposed areas, APA tablets were given twice daily for one week and then three times daily.

Discussion

DR. WALTER F. LEVER: This patient has an unusually large number of soft glistening nodules on his face, especially on the temples, and on the ears and the dorsa of the hands. There has even been bleeding into some lesions, so that they have a purpuric appearance, and it is this that causes considerable resemblance to primary systemic amyloidosis as it occurs on the skin. However, this patient has lesions only in areas exposed to the sun, and that would be unusual in primary systemic amyloidosis.

Histologic examination showed an accumulation of homogeneous fissured masses in the upper dermis which did not stain with Congo red and did not show any metachromasia on staining with toluidine blue. That in itself would not rule out amyloidosis with certainty, because in primary systemic amyloidosis the usual tinctorial responses of amyloid may be missing. Nevertheless, the fact that there was no involvement of the vessel walls and of the glassy membranes around the sweat glands would make me feel that this is probably not amyloid but colloid.

A test one could carry out to decide the matter would be to inject Congo red subcutaneously or intradermally into the vicinity of some of the nodules, because some cases of primary systemic amyloidosis of the skin, in spite of a negative Congo red stain in histologic sections, will show on intravital staining absorption of the Congo red to the nodules. To conclude, I believe that this is an unusual, rather extensive case of colloid milium and not of amyloidosis.

DR. BERNARD APPEL: I should like to ask the histochemists here what their experience has been with a periodic acid-Schiff stain in these cases of amyloidosis. My assumption is that amyloid is a type of polysaccharide, and I wonder what its response is to P. A. S. stain as compared with the traditional stain for amyloid. I have not seen a case of amyloidosis since the use of the P. A. S. stain and should like to hear of somebody's experience with it.

DR. HERBERT MESCON: You can get all variations between the typical things that are described in the textbooks as giving a typical stain for amyloid, on one hand, and homogeneous material that will not stain. Sometimes in the same cases if you take biopsy specimens from involved areas you will not get similar staining. The difference is due in part to the differences in chemical composition and in part to the water-formalin fixation. Much material may be lost, and perhaps formalin vapor fixation

should be used. Very few people will go to that trouble, and this is one of the explanations of the staining variations that occur.

Case for Diagnosis: Mycosis Fungoides; Lupus Erythematosus of the Face with Psoriasis of the Trunk? Presented by DR. MILTON HELMAN.

A man aged 59 is presented from the Massachusetts General Hospital with an eruption of six or seven years' duration. A red, scaly eruption appeared on the body which was benefited by exposure to the sun and was felt to be psoriasis. Five or six months ago an erythematous nonpruritic eruption appeared on the face. It is now occasionally pruritic. Exposure to the sun worsens the facial lesions.

There are infiltrated plaques about the eyes and on the face and eczematous lesions on the trunk.

Urinalysis was normal. The hemoglobin was 15 gm. per 100 cc.; white blood cells numbered 14,900, with polymorphonuclear neutrophils 77%, lymphocytes 9%, and monocytes 7%. A roentgenogram of the chest was normal.

A biopsy specimen from the face is presented. Biopsy of a body lesion was consistent with psoriasis.

Treatment has consisted of chloroquine, 250 mg. four times a day for seven days, three times a day for seven days, and then twice a day for three weeks. There has been no response.

Discussion

DR. JACOB SWARTZ: This is interesting because of the variety of lesions. The man shows some definitely infiltrated lesions that one would not hesitate to diagnose as mycosis fungoides in the tumor stage. He also has lesions that, if they were alone, might be clinically misinterpreted as lupus erythematosus.

I recall a case which was diagnosed clinically and confirmed pathologically as psoriasis. About 10 years later the patient was admitted with an advanced tumor stage of mycosis fungoides. In a case of atypical psoriasis with marked pruritus, one should not be in a hurry to call it psoriasis. Repeated biopsies should be performed.

DR. WALTER F. LEVER: I recall the patient. The diagnosis of psoriasis was made in 1924, and he died with tumor lesions of mycosis fungoides in 1938.

DR. HERBERT MESCON: Was the biopsy specimen here from an infiltrated lesion?

DR. MILTON HELMAN: I saw this man a couple of months ago when he did not have as marked lesions as he has now. Most of those on the face were fairly flat, with some plugging and scaling. The biopsy specimen was from a representative lesion. With the diagnosis of lupus erythematosus from the pathologist, he was given Aralen, without any definite response, and we then tried Plaquenil. The biopsy specimen from the trunk had been reported as consistent with psoriasis. In the first few weeks since he has been taking Plaquenil he has developed many more lesions on the trunk and the lesions on the face have become more infiltrated. Some of the lesions on the top of the forehead today resemble those he had also lower on the face.

DR. WALTER F. LEVER: I entirely agree with Dr. Swartz that this patient has mycosis fungoides, and I think that it is our task to prove that. It can be done only by biopsy, and in such instances where everything depends on histologic examination we should carry out a thorough study by doing multiple biopsies.

As far as the biopsy obtained from the face is concerned, my first impression was lupus erythematosus, because there is hyperkeratosis, follicular plugging, atrophy of the epidermis, and a patchy inflammatory infiltrate which in some areas lies in the vicinity of the appendages, mainly because there are many appendages in the center of the face. However, liquefaction degeneration of the basal layer was not present. In studying the infiltrate, it did not strike me as that of lupus erythematosus, because there were a good many histiocytes, whereas in lupus erythematosus the infiltrate is predominantly composed of lymphocytes.

Unfortunately, I did not find a single atypical cell—no eosinophils—and so I cannot make a diagnosis of mycosis fungoides either on the biopsy specimen from the face. Still, I feel it is just a matter of looking and trying with further biopsies until we establish the diagnosis.

A Case for Diagnosis: Acrodermatitis Chronica Continua of Hallopeau; Psoriasis? Presented by DR. MILTON HELMAN.

A white salesman aged 59 is presented from Beth Israel Hospital with an eruption on the ends of the fingers and toes, with destruction of the nails, which began about 15 years ago. For the past 10 years he has had lesions on the genitalia. The eruption has never entirely cleared, but there have been periods of remission and exacerbation. Various ointments and soaks have been used. X-ray treatment 10 years ago caused no improvement.

The fingernails are broken and discolored, and the surrounding skin is red, scaling, and fissured. There is a similar condition on the toes. The genitals and surrounding skin are red and scaling.

In periods of exacerbation, numerous small, thin-walled, irregularly shaped pustules have been present in the plaques on the genitals and thighs and around the fingers.

Biopsy was consistent with acrodermatitis chronica continua.

Discussion

DR. HARVEY B. ANSELL: Has he lesions on the body? One fingernail I thought rather typical of early psoriasis, and I think that he has psoriasis.

DR. MAURICE M. TOLMAN: When I was a young man I was taught that one saw stippling of the nail. What is the typical early lesion of psoriasis of the nail. If you saw that nail in association with a fungous infection would you still be so positive about its being psoriasis?

DR. HARVEY B. ANSELL: Not positive, but why cannot a person have two diseases?

DR. JACOB SWARTZ: I am one of the teachers Dr. Tolman referred to, and I still feel that only in the stage of pitting, keratotic plugging, and brownish discoloration can one be fairly certain. The more advanced stages of nail involvement in psoriasis cannot be differentiated from onychomycosis without mycologic studies.

I am opposed to the diagnosis of acrodermatitis in this case because of lack of scarring. I feel that the two possibilities are psoriasis and mycotic infection. If the latter, it is probably caused by Trichophyton rubrum, and that explains the nails as well as the lesions on the glabrous skin. I certainly would like to see mycologic studies done.

Case for Diagnosis: Mycosis Fungoides? Presented by DR. BENCEL L. SCHIFF.

A 42-year-old woman states that she developed an eruption of the right breast in 1951 following a hysterectomy. The eruption spread to involve the trunk and buttocks and was accompanied by severe itching. Her health has always been good.

Routine laboratory examinations were negative or within normal limits. Scraping of lesions revealed no fungi. The report on the biopsy was consistent with chronic inflammation. She received topical applications and superficial roentgen therapy, with some improvement of the lesions. However, at no time did the eruption involute completely.

The patient was first seen by me on Sept. 30, 1957, with the eruption involving the breast, abdomen, and lower part of the back.

The lesions on the breast give an orange-peel appearance. The lesions are well-defined, erythematous, oval, confluent, and geographic in outline but show no scaling except on the breast.

Discussion

DR. ARTHUR S. SPANGLER: Clinically it is classical mycosis fungoides. The patient stated that she had had x-ray therapy and that the first time she had improved markedly after one treatment. It was repeated twice afterward, with no change whatsoever. The only diagnostic alternative I can think of is a fixed drug eruption.

DR. C. ROBERT DAMIANI: The lesions were erythematous, well-circumscribed, and not infiltrated. There was also fine scaling. There was no evidence of excoriations, and so I asked her about itching and she replied that there was very little. I feel that this picture is one of parapsoriasis.

DR. ALFRED HOLLANDER: I propose a diagnosis of erythema annulare centrifugum.

DR. JACOB SWARTZ: I think that at present, unless we prove it histologically, we shall have to label this parapsoriasis en plaque, as suggested by Dr. Damiani. We have no right to make a diagnosis of mycosis fungoides without pathological confirmation. It may come later, but until that time we shall have to call it parapsoriasis, especially since there has been very little itching.

DR. ARTHUR B. KERN: The biopsy section reported on was obtained two years ago. I believe that if we obtained one now we would find mycosis fungoides.

DR. MAURICE M. TOLMAN: Apparently mycosis fungoides is not a single picture but a condition which goes through various stages. In thinking of a diagnosis we must trace the entire picture and put it together. Certainly it is my concept that this type of parapsoriasis en plaque, if it is that, is definitely the forerunner of mycosis fungoides. If that is true, we can assemble enough cases to prove the thinking, and the therapeutic approaches will become more clarified.

DR. WALTER F. LEVER: I wish to repeat my plea. We must do more biopsies in these cases where the only worthwhile information can come from histologic examination. When the biopsy is done on these cases, I recommend that not just one specimen be removed but three or four, so that the pathologist has at least a decent chance to arrive at a conclusion.

DR. MAURICE M. TOLMAN: What do we do for a patient like this, aside from making a diagnosis?

DR. BENCEL L. SCHIFF: This patient was seen only once, about two weeks ago, and a biopsy was not feasible at that time. I agree that the biopsy of about two years ago showed no specific histology of mycosis fungoides. I shall perform biopsies of several lesions of the abdomen and shall report at the next meeting.

DR. FRANCESCO RONCHESE: The disorder has been going on for six years. If it is mycosis fungoides it should have changed its clinical appearance and the pathology should show what it is.

DR. MAURICE M. TOLMAN: Some years ago I saw the case of a girl at the Beth Israel Hospital which my senior then showed me as a typical case

of erythema annulare centrifugum. Twenty years later she was in with mycosis fungoides, and so six years is not too long a time. Premycosis fungoides can go on for a good many years before going into the nodular ulcerated stage.

DR. JOSEPH BECKER: Harry Keil wrote an extensive article about parapsoriasis in relation to mycosis fungoides. He feels that every case of parapsoriasis, if it goes on long enough, winds up as mycosis fungoides. How many here believe that?

DR. JACOB SWARTZ: I agree with Dr. Tolman that mycosis fungoides is mycosis fungoides from the onset, but unfortunately it goes through a variety of stages which can simulate parapsoriasis, erythema annulare centrifugum, etc. I also agree with Dr. Lever that repeated biopsies should be done.

DR. ALFRED HOLLANDER: Some cases of parapsoriasis can eventually develop into mycosis fungoides. Also, a cutaneous eruption of long duration diagnosed as true eczema can in reality be premycotic eczema. This patient shows lesions which have not changed whatsoever in about six years. There is no itching. Clinically, these lesions do not appear to be those of premycotic eczema. My first choice is still erythema annulare centrifugum. Repeated biopsies will give the definite answer.

DR. EDWARD A. LAFRENIERE: The case of the man we discussed earlier had a clinical and microscopic picture of psoriasis but now shows new erythematous patches on the body and nodes in the groin and axillas, suggestive of mycosis fungoides. This patient has erythematous patches on the body but no nodes yet, and this is suggestive of parapsoriasis. Biopsy of the skin might help, but such biopsies are not always accurate. Node biopsies should be performed when possible.

DR. EARL A. GLICKLICH: Without a definite pathological diagnosis, would anyone in this group attempt to treat this girl with x-ray therapy?

DR. BERNARD APPEL: I should like to ask Dr. Fromer whether he can treat a small single lesion with the cathode-ray machine?

DR. JOHN L. FROMER: Before I discuss the cathode-ray machine at Massachusetts Institute of Technology I should like to make one comment on the relative value of biopsy in mycosis fungoides. Although in general I would agree with remarks that have been made, I feel that biopsy diagnoses are at times most difficult. In five years we have seen 115 proven cases of mycosis fungoides, and on at least 20% to 25% of these cases you could have used all the criteria mentioned today, sending slides of any types of lesions to anyone, and received equivocal answers. There is no pat diagnosis in mycosis fungoides except long-continued clinical observation. You can get equivocal diagnoses at the same time from two or three biopsy specimens from almost identical lesions. Furthermore, you can get three diagnoses, as we have, in a single patient: (1) chronic dermatitis or eczema; (2) mycosis fungoides, on another lesion on the same chest, and (3) pure lymphocytic lymphoma, from another lesion. These are slides examined by experienced dermatopathologists.

To go back to the first patient, the man, I think that is most likely a case of mycosis fungoides, regardless of the biopsy findings. Dr. Hollander has come the closest to what I would call, clinically, erythema annulare centrifugum, or parapsoriasis, if you wish. I suspect that this patient's biopsies may be either equivocal or negative.

Now, the management of this type of case is a problem. If the biopsies are equivocal, we can shield a single area and give it the equivalent cathode-ray dosage used in generalized mycosis fungoides. If it is mycosis fungoides, the localized shielded area will respond to treatment with the cathode-ray machine. We have never had a failure on the first course of treatment in any of 115 patients. This applies to both the tumor and nontumor stages of the disease.

DR. MAURICE M. TOLMAN: I should like to ask a question and perhaps answer it at the same time, for the sake of discussion, and that is with regard to the early use of either x-rays or the radiomimicking drugs in this stage. We will admit that perhaps the percentage of immediate response is good, but, unless my observation has been poor, sooner or later the lesions return; sooner or later a higher dose is necessary, and before very long comes what is called a radioresistant phase and we have to look for other measures. It has been my policy to make sure that these modalities are withheld from the patient until the time of absolute necessity and to try other measures first. I wonder what the attitudes of the others are.

DR. JOSEPH MULLER: I fully agree with Dr. Tolman. I think that to give this patient, now that she is subjectively well, a cathode-ray treatment would be ill advised.

DR. JOHN L. FROMER: I would not subject this patient to over-all cathode-ray therapy. We are discussing the use of a shielded area for a trial of therapy, just as we would with conventional x-rays, which I have always believed was accepted practice in lymphoma cutis.

As far as recurrences are concerned, that is an entirely different matter. Of course, no one today knows of any modality which is permanently effective in cases of lymphoma of any type—chemotherapy, ionizing radiations, or any sort of therapy. The recurrence rate is exceedingly high. In fact, we have stopped talking about recurrences in lymphoma cutis. We talk about salvaging the patient. At present the longest survival of a pa-

tient who already had tumors is four years with use of cathode-ray therapy.

DR. JACOB SWARTZ: I want to second every statement Dr. Tolman has made, because I have strong feelings on the subject. I have seen these cases of mycosis fungoides which were radioresistant because they had had a lot of treatment when it was not necessary, when we could have waited till they really needed it. I should like to ask Dr. Fromer a question: Suppose you did shield one area and that area cleared; would that help you to make a diagnosis of mycosis fungoides without the histologic picture and without the characteristic clinical picture?

DR. JOSEPH GOODMAN: It is not clear to me whether radioresistance is induced by x-ray treatment or other modalities or whether it is in the nature of the disease itself that eventually it does not respond to x-rays. If the latter is the case, then there can be no harm in giving x-rays, but if x-ray therapy induces resistance, then the patient should not be treated.

DR. JOSEPH BECKER: Since steroids are now beginning to be used in the treatment of specifically x-ray-resistant Hodgkin's disease, how about trying steroids first in this disease?

DR. MAURICE M. TOLMAN: I have shown these cases before this society last year and before, and one was the case Dr. Mescon diagnosed for us in which we gave cortisone and did bring about a remission, which may have been spontaneous. We have no baseline to prove it. I think that if you treat the disease in the eczematous stage or the exfoliative erythroderma stage with pruritus a trial with steroids is indicated long before one would resort to pushing an electric button.

DR. MAURAY J. TYE: I should like to know about the cases Dr. Fromer mentions as "having gone into long remissions." Were those cases treated early, as this one, or were those cases that had extensive lesions? Is there any pattern to those who remained in remission?

DR. JOHN L. FROMER: Most of the patients we have treated have had extensive x-ray therapy elsewhere. They have gone through the pattern of parapsoriasis, psoriasis, eczema, and drug eruption, the entire gamut of dermatologic disease which has to be considered in the differential diagnosis of mycosis fungoides. Most of our cases are in either the plaque or tumor stage before we get them.

DR. MAURAY J. TYE: Have you treated any like this?

DR. JOHN L. FROMER: Once the diagnosis of mycosis fungoides has been established, one cannot see a definite pattern of response. As I said before, they will all respond on the first course of therapy, which takes from four to six days. One cannot predict from the stage of the disease how long they will stay in remission or how soon they will have to be retreated. We have been surprised with some patients who have disappeared after treatment for 8 to 10 months; they write us and say that they are getting ultraviolet therapy or similar banal therapy and are still in remission. A few patients who have never had previous ionizing radiations have seemed to do exceedingly well with cathode rays. I do not believe that we have any evidence to show that x-rays induce resistance. The individual host response seems to be the determining variant.

DR. ALFRED HOLLANDER: I do not believe that mycosis fungoides becomes resistant to x-rays only. Regardless of the type of radiation which has been administered, any case of mycosis fungoides eventually will not respond to any type of radiation any more.

Case for Diagnosis: Sarcoidosis? Presented by DR. BERNARD APPEL.

Tuberous Sclerosis with Adenoma Sebaceum. Presented by DR. WALTER F. LEVER.

Congenital Ichthyosiform Erythroderma. Presented by DR. WALTER F. LEVER.

Pigmented Flat Nonhairy Nevus. Presented by DR. FRANCESCO RONCHESE.

Minimal Pulmonary Tuberculosis (Arrested); Lupus Milaris Disseminatus Faciei; Lupus Erythematosus? Presented by DR. EARL A. GLICKLICH.

Porphyria Cutanea Tarda, with Cirrhosis of the Liver. Presented by DR. MAURICE M. TOLMAN.

Case for Diagnosis: Allergic Vasculitis? Presented by DR. ARTHUR S. SPANGLER.

Keratosis Follicularis. Presented by DR. MILTON HELMAN.

Lichen Nitidus. Presented by DR. MAURICE M. TOLMAN.

Pemphigus Erythematosus. Presented by DR. HERBERT MESCON.

Case for Diagnosis: Pemphigoide; Erythema Multiforme? Presented by DR. HERBERT MESCON.

Chronic Discoid Lupus Erythematosus (Hypertrophic Type). Presented by DR. DAVID W. FOLAN JR.

Melanosis, Probably Secondary to Hemochromatosis or Cirrhosis. Presented by DR. MCCARTHY.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by DR. JOHN ADAMS JR.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by DR. MAURICE M. TOLMAN.

Syringocystadenoma. Presented by DR. ROBERT F. TILLEY.

Keratosis Follicularis. Presented by DR. FRANCESCO RONCHESE.

Porphyria Cutanea Tarda. Presented by DR. MAURICE M. TOLMAN.

Discoid Lupus Erythematosus. Presented by DR. HERBERT MESCON.

Case for Diagnosis: Nonspecific Dermatitis. Presented by DR. FRANCESCO RONCHESE.

Case for Diagnosis: Sarcoidosis? Presented by DR. BERNARD APPEL.

THE NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILOLOGY

Jack Wolf, M.D., Chairman
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Porphyria Cutanea Tarda. Presented by DR. DOUGLAS TORRE.

From: New York Hospital.

Duration: One year.

Sites: Extremities and midchest.

History: A 54-year-old woman, a clerk-typist, first noted the appearance of vesicles on the dorsa of the fingers and hands one year ago. In the past few months the vesicles have become more numerous and larger and have appeared on the forearms and feet as well as the hands. Pruritus has become severe and includes the upper anterior chest. Five months ago an episode of fever, weakness, generalized aching, sore throat, and diarrhea was treated by injections of penicillin and an unknown oral medication. Edema of the ankles appeared at that time and has persisted to the present. Diuretics were administered. The symptoms subsided somewhat, but four months ago pleuritic symptoms appeared, accompanied by fever and night sweats. For the past three months her urine has been reddish in color.

There has been no association of appearance of lesions or symptoms with exposure to the sun.

Family history is noncontributory. Patient has two sisters who will be tested for porphyrins.

Examination shows a well-developed well-nourished white woman who looks older than her stated age. The skin is darkly pigmented, particularly on the exposed areas of the face. Slight hypertrichosis is present. Symmetrically over both hands, forearms, and feet are vesicular and bullous lesions. The midanterior chest shows some excoriations.

Laboratory examination gave the following results. Urine: bile, negative; urobilinogen, 1.8 mg.; porphyrobilinogen, negative; porphyrin, strongly positive. Blood: L. E. preparations, negative; protein, 6.0 gm. per 100 cc.; albumin, 3.8 gm. per 100 cc.; globulin, 2.2 gm. per 100 cc.; bilirubin, 0.6 mg. per 100 cc. (direct 0.1, indirect 0.5); serology, negative; sedimentation rate, 18 mm. in an hour.

Discussion

DR. S. GRANICK (Rockefeller Institute): Today we saw a patient who had skin lesions on the exposed parts of the body and whose urine fluoresced pink in Wood's light. This patient has one of the rare types of inheritable diseases of porphyrin metabolism. There are two kinds of these diseases which may come to the attention of the dermatologist, because, in both, porphyrins accumulate in the skin and lead to photosensitivity on exposure to visible light, resulting in more or less severe skin lesions.

One kind is "congenital porphyria." This is Mendelian recessive; it appears before the age of 2 and is severe. The metabolic lesion is in the bone marrow. The red cells are fragile, and so anemia may be present. The porphyrins deposit in bones and teeth; the teeth fluoresce pink in Wood's light. The pink urine fluoresces pink or red in Wood's light and has typical absorption bands of porphyrins which are predominantly of the Isomer I type.

The other porphyria is "cutanea tarda"; it appears generally after puberty or in early adulthood and may be mild. The metabolic lesion is in the liver. Severe damage may be observed as a heightened Bromsulphalein retention. In Wood's light, the urine fluoresces pink, and it has typical absorption bands of porphyrins or zinc porphyrins which are a mixture of Isomer Types I and III.

DR. ALEXANDER A. FISHER: As far as therapy is concerned for this group of interesting cases, there have been some encouraging reports with the use of Aralen, or chloroquine. On the other hand, one author reported a case in the A. M. A. ARCHIVES OF DERMATOLOGY in which he claimed that the Aralen precipitated the porphyria. (Davis, M. J., and Vander Ploeg, D. E.: Acute Porphyria and Coproporphyrinuria Following Chloroquine Therapy, A. M. A. ARCH. DERMAT. 75:796 [June] 1957).

DR. CARL T. NELSON: It should be pointed out that the cutanea tarda type of porphyria is 40 times commoner than the congenital type. This patient was of some interest to me because she showed no sclerodermatous changes and no hypertrichosis, features which one might expect in this type of case. It was also my impression that liver damage is usually severer than that shown by this patient. Moreover, this patient gives no history of a high intake of drugs (particularly barbiturates or alcohol), which one might expect in cases of this sort.

DR. DAVID BLOOM: It is of interest that, while the congenital type of porphyria is recessive in inheritance and is partially limited to the male sex, the acute and intermittent is dominantly in-

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herited and favors the female sex. It is of importance to know that the urine does not show any fluorescence when porphyrobilinogen only is present. It requires, then, chemical examination of the urine for uroporphyrin. The late type of porphyria is often associated with abdominal symptoms simulating appendicitis or any other surgical abdominal condition. A number of such patients have been operated on more than once until the diagnosis of porphyria was made.

DR. MAURICE J. COSTELLO: I was impressed by the fact that one of the previous speakers said that this patient had lesions on the face. I did not see any there. If there were, they were extremely minimal, unless he considers the increase in hyperpigmentation and the hypertrichosis part of that picture. There could be some difficulty in differentiating this chronic type from the acute type. In the acute type one sees scarring. In this particular case I doubt very much if this patient will have any scarring at all. One would be hard pressed to differentiate this from erythema multiforme or other bullous diseases. The pinkish fluorescence in the sebaceous material seen in the follicular opening is due to porphyrin.

DR. GERALD F. MACHACEK: It has also been my impression, although I have not experienced this, that the porphyria may be accompanied by definite and severe neurologic changes with actual pathology. I wish someone who has had some experience would discuss that element.

DR. DOUGLAS TORRE: Thank you for the discussion. It is interesting to note that when this patient was studied in the diagnostic clinic porphyria was suggested as a clinical diagnosis. The hospital laboratory, however, performed only the porphyrin precursor evaluation (porphyrobilinogen), which was negative. In cases like this merely testing the urine for fluorescence with Wood's light would establish the diagnosis.

Scleroderma with Follicular Dermatitis of the Face. Presented for diagnosis of dermatitis of the face by DR. HARRY J. KATZ.

From: New York Hospital.

Duration: Three years.

Site: Face.

History: A 37-year-old white woman was hospitalized at New York Hospital in October, 1956, complaining of a 70 lb. weight loss over a period of two years, a rash on her face, and muscle pains and blueness and coldness of her hands and feet, all having been present for two years prior to admission to the hospital. A diagnosis of scleroderma was made on the basis of the x-ray studies of her esophagus and of a muscle biopsy. No diagnosis was made of her facial dermatitis, which has persisted.

Examination shows that the patient presents a maculofollicular acneform dermatitis with erythema involving the entire face. Skin of her fingers is thickened, and underlying tissues are hard. Right hand cannot be clenched completely.

Laboratory examination gave the following results: Hb, 11.00 gm. per 100 cc.; RBC, 4,200,000; WBC, 9500; hematocrit value, 41%. Five L. E. preparations of the bone marrow have been negative. X-ray of esophagus is characteristic for scleroderma. Findings on biopsy of facial lesion show nonspecific folliculitis.

Course: There has been no improvement or change in the facial dermatitis. The sclerodermatous condition of the hands and forearms has remained unchanged.

Discussion

DR. ADRIAN NEUMANN: I think that the patient has both scleroderma and acne rosacea.

DR. J. LOWRY MILLER: I should agree that this is a case of acrosclerosis, with the classical symmetrical involvement of the hands. I am not so certain that this is just rosacea on the face. I cannot offer a better diagnosis than a folliculitis of the face.

DR. JOSEPH L. MORSE: Was this patient getting cortisone?

DR. HARRY J. KATZ: No.

DR. JACK WOLF: This patient's general condition warranted a routine gastrointestinal series, which was done on admission to the hospital. It was on the basis of the roentgenographic findings, the esophageal sclerosis, that the diagnosis of scleroderma was made. Involvement of the fingers came at a later date.

DR. MAURICE J. COSTELLO: I should agree with the presenting diagnosis, acrosclerosis, and I agree with the others who think that she also has rosacea. That could be easily proved by giving her the specific treatment for rosacea, 3% each of salicylic acid, sulfur precipitate, and unguentum quinola compound in enough unguentum Aquaphor to make 30 gm.

DR. ARTHUR B. HYMAN: This patient has scleroderma. That we all agree, but the eruption that the woman has on her face could hardly be called follicular. She has scattered excoriated papules. It would be unfair to incriminate the follicular osteum, only, for the location of the lesions. They are irregularly scattered, and with a multimagnifying glass some may by chance prove to be follicular. There is an unfortunate tendency to describe papules as follicular even if they are not so. There was not anything particularly rosaceous about the eruption, and there was no erythema with pustulation which is fairly limited to the midline of the face, such as one

finds in rosacea. I should suggest that the patient has neurotic excoriations on the top of scleroderma. The woman, suffering as she does, as miserable-looking as she is, should not have added a further measure of misery to her sad state by powerful methods of treatment.

DR. JACK WOLF: The Chairman humbly admits that he saw this patient in private practice on several occasions and did not cure her. I did have the opportunity of following the course of the papular and pruritic eruption on the face, which was also present on the outer aspects of the arms. There was no resemblance at any time to an eruption that could be even remotely related to rosacea. The eruption was papular and intensely pruritic and could not be classified beyond that. The lesions were not neurotic excoriations; whatever excoriation was present was secondary to the main process. Tonight I think that this patient presents a papular and pruritic eruption, possibly a neurodermatitis not directly related to the scleroderma as such but as an emotional reaction to the scleroderma.

DR. CHARLES WOLF: Since the facial eruption is eclipsing the systemic eruption, I should like to inject another phase in which the diagnosis of the eruption on the face is different from any that has been rendered so far, and that is a halogen sensitivity in this person. This was ascertained through the means of asking her how much salt she consumes; the answer was that she uses an excessive amount of it, and, therefore, the eruption in my opinion is a halogen sensitivity, a sensitivity particularly to iodine.

DR. HARRY J. KATZ: We have been frankly puzzled about the case. Some men at our hospital have considered it to be rosacea, and we have made the tentative diagnosis of rosacea.

I might add that the dermatitis started simultaneously with the symptoms of scleroderma. The x-ray men and the medical department associated her gastric distress with the sclerodermatous changes in the esophagus.

We have given no treatment for the dermatitis.

DR. JACK WOLF: May I say that her condition did improve with steroids early in the course, when I had occasion to see her.

DR. HARRY J. KATZ: We did not have that on the record.

Sarcoidosis (Boeck). Presented by DR. THOMAS GRAHAM for DR. HERBERT SPOOR.

From: New York Ear and Eye Infirmary.

Duration: Two years.

Locations: Face (right eye, lips), arms, legs.

A 24-year-old single Negro girl's first symptom of her present condition was an irritation of the right eye in August, 1955. The condition was diagnosed as conjunctivitis; it was treated with ophthalmic cortisone preparations and cleared completely within three weeks. Shortly thereafter one or two papular lesions appeared on the arms. These persisted, and then in December, 1956, similar lesions occurred all over the face and body. In August of this year the right eye became involved again, and at this time the lesions of the lips that are now prominent began to appear. The lesions tend to disappear spontaneously, leaving depigmented, but not atrophic, sites. The facial lesions are of most concern to the patient and infirmary staff.

System work-up gave the following information. Eye: Conjunctivitis right eye, nonresponsive to therapy; biopsy specimen from cystic lesion beneath eye—suggestive of xanthelasma. Ear: Noncontributory. Nose and throat: Sinus x-rays Aug. 12, 1957, showed that both frontal sinuses were clear; that the right ethmoid was slightly clouded; that both antra were hazy and there was a suggestion of mucosal thickening in the floor of the right antra, and that the sella appeared normal. Dental examination: All teeth clear except abscessed second molar; tooth removed Aug. 19, 1957. Chest: X-ray taken Aug. 12, 1957, shows basal breast clouding; hilar regions thickened, with dense radiation extending superiorly and inferiorly; cardiovascular shadow normal. The conclusion was that there was marked bilateral hilar thickening. Repeat x-ray, for depth, taken Aug. 15, 1957, showed that there had been no change since Aug. 12. Outstanding finding was marked hilar thickening, with dense fibrosis extending toward base.

Laboratory examination on Aug. 12, 1957, gave the following results. Serology (VDRL) negative. Tuberculin negative. Febrile agglutinations—typhoid "H" +1/20, +1/40; all other negative (typhoid O; paratyphoid A, B; Proteus OX_{19}; Brucella abortus). CBC: RBC 4,400,000; WBC 4900, with polymorphonuclear leukocytes 56%, lymphocytes 34%, monocytes 4%, eosinophils 5%, and basophils 1%. Blood glucose 78 mg. per 100 cc. Urine normal.

Skin biopsy of specimen from the right forearm taken Sept. 3, 1957, showed a pigmented but essentially unaltered epidermis overlying a dense dermis in which there were foci of inflammation. There were discrete nodules composed of epithelioid cells, which were small and uniform. Some cells appeared to be undergoing necrosis, while others suggested plasma-cell formation. In spite of this there was practically no reaction of the surrounding tissue. These areas were compatible with and

suggestive of Boeck's sarcoid but were not diagnostic of it. Diagnosis: granuloma of epithelioid type compatible with Boeck's sarcoid.

Discussion

DR. HERBERT SPOOR: There is not a great deal more to discuss on the case from our standpoint. The original signs were conjunctivitis some two years ago. The return visit to the hospital this summer was for a repeat episode of conjunctivitis. The first time it cleared up completely with cortisone therapy. The second time nothing touched it at all. The sarcoid-like lesions are spreading and causing the patient quite a little distress. The chest film, which I unfortunately could not bring, certainly confirms the presumptive diagnosis of sarcoid.

DR. DAVID BLOOM: This patient presents true sarcoidosis as seen in the white race and rarely seen in the Negro. The majority of cases presented as so-called sarcoidosis in the Negro are, I believe, not identical with true sarcoidosis, but are an attenuated type of tuberculosis rarely seen in white patients.

DR. CHARLES WOLF: I should like to ask the presenter whether or not an ophthalmological examination was made in this case.

DR. HERBERT SPOOR: It certainly was, but I cannot give you the detailed findings. The consensus of opinion of the eye men was that there is nothing present here at this time except conjunctivitis—no iritis or retinitis. That will be expected to develop later.

DR. CARL T. NELSON: Despite the report of the ophthalmologist, I think that this patient has more than conjunctivitis. She has iritis, and, if she does not now have severe uveitis, she will have it shortly unless treatment is begun soon.

While I am not a strong advocate of the use of corticosteroids in the treatment of sarcoid, there are at least two definite indications for their use in this disease. One is eye involvement, and the other is severe pulmonary insufficiency. Sarcoidal involvement of the eye is so devastating that treatment with large doses of corticosteroids is warranted. This patient should have large dosages by mouth, since it is likely that local hydrocortisone will prove to be inadequate in preventing loss of vision.

DR. HERBERT SPOOR: The patient was seen last Friday by the eye doctors, and the decision of the staff then was that in view of the chest film the possible danger of cardiac failure following corticotropin or cortisone therapy (in this particular case) made them hesitant about using heavy dosages of steroids.

Localized Myxedema. Presented by DR. DOUGLAS TORRE.

From: New York Hospital and Memorial Hospital.

Sites: Hands and feet.

Duration: Two years.

History: A 75-year-old Polish shoemaker was treated for hyperthyroidism with malignant exophthalmos by administration of 6.8 mc. of I^{131} in December, 1953. Signs of myxedema (weight gain, progressive easy fatigability) were subsequently noted, and so thyroid hormone was administered to maintain the patient in a euthyroid state. In 1955 thickening of the skin over the hands and feet was first noted. Pruritus was severe. The condition has become progressively worse.

Treatment has consisted of thyroid hormone, triiodothyronine, and cortisone systemically. Hydrocortisone and hyaluronidase were injected locally, and triiodothyronine (Cytomel), applied by inunction. Antihistamines and Serpasil have been given for symptomatic relief.

Examination shows that symmetrically over the extremities the skin is thickened in irregular firm plaques. Exophthalmos is present.

Laboratory examination showed Congo red test negative for amyloidosis.

Findings on biopsy indicated myxedema.

Discussion

DR. ARTHUR B. HYMAN: In a sense this is a straightforward example of so-called circumscribed myxedema associated with exophthalmos. It is apparently the same type of mucinoid material which in the orbit produces exophthalmos that is responsible for the lesions in the skin. The skin lesions are found regularly in association with exophthalmos following thyroidectomy. A significant very recent finding is that there is an increase in acid-soluble mucoproteins in the blood.

DR. FRANK E. CORMIA: I shall not question the diagnosis. I know that Dr. Torre has investigated the case thoroughly; however, the eruption does not look like any localized myxedema that I have seen. It looks more like amyloidosis but is not typical for that disease. I should suggest further studies. Toluidine blue stains the polysaccharides and would show the presence of mucin. There should be further tests to rule out amyloidosis.

DR. DAVID BLOOM: The appearance of the eruption particularly on the legs suggests strongly the diagnosis of myxedema. I should like to ask the presenter whether hyaluronidase injections have benefited the patient. In a few cases I have seen good results from this type of treatment.

DR. GERALD F. MACHACEK: No one mentioned the common observation of myxedematous lesions

occurring with hypothyroidism. As far as hyaluronidase is concerned, although it is of some benefit, there is almost equal benefit to the patient from bandaging the extremity.

As to malignant exophthalmos, that may appear after the hypothyroidism presumably is relieved to a great extent. I do not think that there is agreement on what is the mechanism of this. There is only agreement that mucoid or mucinous deposit is present. There are those who feel that perhaps there is also a question of degeneration of muscular tissue. Many questions can be asked. It is certainly an interesting phenomenon which appears in this condition, and the administration of thyroid certainly does not help. It is a very unfortunate state of affairs, the exophthalmos following even the operation on the orbit done in order to relieve the condition.

DR. ARTHUR B. HYMAN: As Dr. Machacek said, there is much to be elucidated in this problem. This is true, but there is also much that has already been elucidated in the pathogenesis of this condition. It usually develops after thyroidectomy, whether the effects of the thyroid have been removed by surgical excision, thiouracil or its relatives, or radioactive iodine. The thyroid is an antagonist to the pituitary exophthalmotropic hormone. When this antagonist is removed, the exophthalmotropic hormone produced by the pituitary results in the deposit of a mucinoid material in the orbit and, here, in the legs. Therefore, the disease follows thyroidectomy in these patients and is due more directly to a pituitary hormone and only indirectly to a disturbance of thyroid hormone.

DR. IRVING ABRAHAMS: There was an article very recently in the *A. M. A. Archives of Internal Medicine* (August, 1957) that described successful therapy with local injection of triiodothyronine. The protocol in the case tonight mentioned the use of triiodothyronine by inunction. The internist used the method of therapy described with remarkable remission of the local lesion within 48 hours after injection of 0.4 mg. of triiodothyronine.

DR. DOUGLAS TORRE: As Dr. Cormia said, the picture here is not completely clear, and we did think of amyloidosis before studies were made. The Congo red test was negative, and the biopsy did not support amyloidosis, and so we felt we were on safe ground in calling this myxedema, particularly as exophthalmos was present.

As far as therapy is concerned, this patient has received injections of hydrocortisone and hyaluronidase without benefit. Triiodothyronine was used systemically by the oral route and by inunction. It was not used by injection. That is a very good suggestion, and we will try it.

Lichenoid and Exudative Neurodermatitis.

Presented by DR. FRANK E. CORMIA for DR. MARK MARCIANO.

From: New York Hospital.

Duration: Twenty-four years.

Sites: Generalized.

History: A 57-year-old elevator operator developed a vesicular dermatitis of the hands 24 years ago. It persisted for two years, and then a seborrheic type of dermatitis involved the axillae. Shortly afterward and following marriage, dermatitis developed on the scalp, the face, the ears, and the antecubital, popliteal, and genital regions. Subsequently, mild erythroderma supervened. The eruption has been continuously present to date with exacerbations and partial remissions. In exacerbation, the ears and genital region have been most severely affected. These and other areas then became the site of a moderate edema, exudation, and crusting.

Through the years the eruption has been well correlated with the inability to attain a life position commensurate with his ambition and with a great deal of domestic tension. This has been potentiated by a poorly adjusted and somewhat paranoid wife and a daughter (now 21) who has been extremely difficult to manage. The eruption has been further aggravated by heat, humid weather, the effects of sweat retention, and the intervention of a mild secondary infection.

Various types of therapy have been employed, including x-rays to tolerance, ultraviolet rays, antihistaminics, systemic and topical steroids, tranquilizers, sedatives, and innumerable forms of local therapy. Improvement from these measures has been temporary. Four years ago, while the patient was taking small doses of cortisone, a duodenal ulcer supervened. After this initial attack, it has given him only a slight discomfort. For various reasons psychotherapy has never been attempted.

Examination shows mild generalized erythroderma with a lichenoid overlay and an exudative eczematous process noted chiefly on the ears, genital region, adjacent thighs, and presacral area.

Laboratory examination was negative, except for x-ray evidence of duodenal ulcer.

Findings on biopsy showed that the epidermis is covered by a parakeratotic crust and tremendously thickened in regular fashion. The basal-cell margin is intact. Vessels of the upper cutis are dilated and thickened and surrounted by increased edema and a mantle of lymphocytes, plasma cells, and histiocytes.

The findings on two previous occasions were similar (three and eight years ago).

This patient is presented for a discussion of the etiology of this syndrome and for opinion on the possible value of psychotherapy.

Discussion

DR. GERALD F. MACHACEK: I should be rather emotionally upset if I had such a generalized eruption. I do not say that perhaps it does not pay this man in some way or other to be sick, but it is always to me a sign of defeat on the part of the physician who so easily passes these things off to a psychiatrist even up to the point of, on occasion, giving the patient shock treatment.

DR. VICTOR H. WITTEN: If we were to choose sides, I guess we would have representatives for each side of this discussion—those who favor psychic trauma as a cause for the episodic flare-ups and those who would say that it probably has no real connection. I do not think that the presenter here meant to say that this disease was definitely due to psychic trauma, but when there was failure to respond to therapy, including corticosteroids and the like, he only then began to wonder if that might not be the situation. It is necessary, however, to consider seriously the possibility of this being a chronic dermatitis of a seborrheic variety, perhaps psoriasiform, and also the possibility of an allergic contact dermatitis. Unfortunately, even the most exhaustive studies of these patients often leave us with no definite answer as to the etiology. This makes for an unhappy situation, as we are tempted, and it becomes so easy, to turn to the psychosomatic cause of disease. As to the choosing of sides, I stand on the side that favors a cause other than the psychosomatic.

DR. ARTHUR B. HYMAN: I would support Dr. Witten's thesis that this is not of psychic origin. This patient has erythroderma in the exudative stage, with atrophy. This is not a feature of distinctive exudative discoid chronic lichenoid dermatosis. Also he did not have the sharp defined recalcitrant lesions on the penis such as one usually finds associated with the putrefactive disease.

DR. CHARLES WOLF: This case has gone the rounds through the years, and the history in this case is the most important part of the etiology from the standpoint that this man is improved when he is away from his environment. For instance, when in Arizona and California he was a great deal improved. His family life is one of a great deal of egritude (mental anxiety, worry and other tribulations that he has). He told me that his daughter is a deaf mute, and as the result of the handicaps that this young person encounters there is constant dissension in the home life. From the innuendo in the last sentence of the protocol, which asks, "Is this a psychotherapeutic case" I should say it certainly is.

DR. PAUL GROSS: It is surprising that we are still having to discuss this interesting disease which has been so well described by Sulzberger and Garbe. For the psychosomatic implications of this disease, I would refer you to the papers of Dr. Beatrice M. Kesten and Elias Schneider which appeared years ago in the *Journal of Investigative Dermatology* under the title "Polymorphic Prurigo." Even at the risk of disagreeing with Dr. Sulzberger, I consider this disease one of the best examples of a psychogenic dermatosis.

DR. ADRIAN NEUMANN: A few years ago I had a case which closely resembled the one we saw tonight. The patient's generalized lichenoid and exudative dermatitis cleared spontaneously each time he left his home for a few weeks but recurred to the same extent after he was at home again for a few days. It was my belief at that time that the cause was psychogenic in origin. One day I was called to the patient's home; intense fumes emanating from a kerosene stove struck my nose. On my suggestion, the patient and his family moved to a more modern apartment, and within a short time his dermatitis cleared completely and permanently. A subsequent patch test with kerosene confirmed my diagnosis of contact-type dermatitis rather than dermatitis elicited from psychogenic factors.

DR. FRANK E. CORMIA: We have considered this eruption as psychogenic and have had the patient under observation for several years. He has not had psychotherapy, since this would certainly not rectify the intolerable home situation.

Case for Diagnosis: Hypertrophic Lichen Planus; Neurodermatitis? Presented by DR. ANTHONY CIPOLLARO for DR. MARK MARCIANO.
From: New York Hospital.
Duration: Four years.
Site: Medial aspect of right leg.

History: A 41-year-old housewife was first seen in the Dermatology Clinic five months ago with a pruritic thickened violaceous scaly lesion on the medial aspect of the right leg. The patient has been treated with various salves without improvement.

Past history reveals that the patient has had asthma since the age of 16 and was hospitalized for atopic dermatitis, in 1949, 1950, and 1951. The drug history is negative.

On examination the medial aspect of the right lower third of the leg reveals a linear hypertrophic violaceous plaque, measuring 1 cm. by 5 cm., covered with adherent dry white scales, and firm to the touch. The mucous membranes are free of lesions.

Laboratory examination of blood and urine gave normal values.

Findings on biopsy showed that there is hyperkeratosis and psoriasiform acanthosis. Blood vessels are dilated and thickened, and scanty inflammatory reaction surrounds them.

Diagnosis: Neurodermatitis (psoriasiform); could be prurigo.

Discussion

DR. PAUL GROSS: This is a very good example of a solitary lesion in a case of lichen simplex chronicus but not of lichen planus.

DR. ANTHONY N. DOMONKOS: I suggest therapy with the local injection of prednisolone suspension.

DR. MAX WOLF: This case presents the features of a hypertrophic linear neurodermatitis along the course of the origin of the saphena magna. Cirsoid varicose veins above the lesion are leading to the pruritic patch. I think that the localized neurodermatitis can be cured by elimination of the incompetent feeding "key vein" and by improvement of the deficient circulation (see *Arch. Dermat. & Syph.* 52:376-383, 1945).

DR. ANTHONY CIPOLLARO: A case like this is presented because of the difficulty of diagnosing it. The diagnosis which was given by Dr. Gross is probably the correct one. The histologic picture is that of psoriasiform neurodermatitis. The clinical appearance of this eruption simulates lichen planus of the hypertrophic type. Sometimes psoriasis resembles neurodermatitis.

DR. MAX BRAITMAN: Several men tonight have referred to the use of Meticorten injection locally in dermatitis. I have not had any experience with atrophy following its use. I would appreciate comments from others as to such findings.

DR. EDWARD H. MANDEL: I have had some experience with this. I can say that in some patients you will get definite atrophy of the subcutaneous tissue.

DR. ANTHONY N. DOMONKOS: I should like to say that I have also used injections for cases of alopecia areata, with the scalp receiving at least 50 injections. Five months later I was not able to tell where the injection had been, with the exception of one or two spots where hair was growing. There is no atrophy present clinically.

DR. VICTOR H. WITTEN: Our experience is similar to that of Dr. Domonkos. Following the local intradermal injection of hydrocortisone acetate, there is a palpable depression at the site of injection. While I am not sure of the frequency, in many instances there is return of tissue substance in these areas.

Congenital Hyperkeratosis of the Palms and Soles (Mal de Meleda?). Presented by DR. FRANK CORMIA for DR. ROBERT ABEL.

From: New York Hospital.

Duration: Twenty-eight years.

Sites: Palms and soles.

History: A 28-year-old typist has always been in good health. At the age of 8 months it was first noted that she had thickening of the palms and soles. Starting with the thumbs, the skin became thick and waxy and less flexible. This condition spread to involve the palms and soles. Occasionally there would be some peeling of the skin. She has been treated with many salves, with no improvement. There has been no change with maturity, weather, diet, etc.

Family history: Both parents are of Italian ancestry. There is no family history of similar disorders.

Examination shows the palms and soles and some of the dorsal aspects, especially over the joints, covered by thick yellow waxy skin. There is slight erythema over the edges of the lesions on the dorsum of the hand.

On laboratory examination, culture from nails showed Aspergillus glaucus.

Discussion

DR. SIMA ILICH (Belgrade, Yugoslavia): I am very glad to have the opportunity to speak here at the meeting of the Section on Dermatology of the New York Academy of Medicine. This seems to be a duplicate of a typical case of mal de Meleda. The changes are not only on the soles and palms but also on the dorsum of the foot and the dorsum of the hand.

It is very interesting to know that the patient comes from Sicily, an island off the west coast of Italy. In the island Mljet, on the east of Italy, as you know, we have this disease as an endemic one. It would be interesting and I would suggest Dr. Cormia do some research in this island, particularly in the district from which the girl comes, and study it epidemiologically and geneologically. I think that this is a typical case of mal de Meleda (Mljet).

DR. DAVID BLOOM: I believe that mal de Meleda is nothing else than keratoderma palmare et plantare with additional hyperkeratoses on the extensor surface of the extremities. I think that it is very questionable to consider mal de Meleda as a special entity. The recessive inheritance reported in some of such cases is uncertain.

DR. FRANK CORMIA: I am sorry that therapeutic suggestions were not made. To date, our treatment has been a complete failure, but it is an amazing thing that this woman is able to carry on with her work despite the very marked hyperkeratotic process on her hands.

Pityriasis Rubra Pilaris. Presented by DR. DOUGLAS TORRE.

From: New York Hospital.

Duration: Ten years.

Sites: Generalized.

History: A 40-year-old man, a commercial artist, first noted a patchy roughness of the skin.

Later, circinate lesions which enlarged peripherally and had elevated margins appeared.

Past history reveals normal development to the age of 12. Between 12 and 14 he gained 50 lb. and felt physically sluggish, although mentally he was 3 to 4 years advanced. Between the ages of 12 and 23 he gained only 2 in. in height. He developed gynecomastia, which was treated surgically in 1946. From 1940 to 1947 he was under observation in the endocrine clinic with the diagnosis of adrenal hyperplasia. Repeated examinations revealed 17-ketosteroids to be at a high level (20 to 24 mg.). Treatment at that time consisted of administration of thyroid, pituitary, and androgenic hormones. Vitamin A has been administered for the skin condition.

Examination shows that the patient is well developed but with short stature and somewhat feminine fat distribution. Striae are present. The skin shows irregular areas of roughness in which small spicules can be felt extending from the follicular openings.

Findings on biopsy show that throughout the cutis there is a diffuse inflammatory reaction of small round and wandering connective tissue cells. In one section there is dilation of the follicle walls. The walls are acanthotic, and the lumen is filled with an increased densely laminated horny layer. There is a moderate inflammatory reaction about this follicle. Lichen planopilaris, keratosis follicularis, and keratosis pilaris can be ruled out. There is an increased cellular reaction. There is no spinous process, and so lichen spinulosus is ruled out.

Diagnosis: Keratosis rubra pilaris or avitaminosis.

Discussion

DR. ORLANDO CANIZARES: I am sorry to disagree with the diagnosis. I frankly did not think that, clinically at least, this patient presented the characteristics of pityriasis rubra pilaris. He has some very small spines in some of the lesions that would fit in a diagnosis of lichen spinosum. He does not present any of the papules on his hand or anywhere else which are classical in this disease. Besides, there is no redness, which is one of the fundamental characteristics of pityriasis rubra pilaris.

DR. GERALD F. MACHACEK: I agree with Dr. Canizares. So often pityriasis rubra pilaris may have a real psoriasiform effect. Also there are dome-shaped papules with the keratinitic inclusions within the center. Another peculiarity was the very extensive striations, which looked like ferns. I understood from the history that there is hyperadrenalism. Is that correct? I disagree with that.

DR. ARTHUR B. HYMAN: I do not agree with the diagnosis of pityriasis rubra pilaris. There is neither hyperkeratosis of the palms, nor map-like lesions on the chest and back, nor any seborrheic dermatitis-like eruption of the scalp. In any case nobody knows the cause of pityriasis rubra pilaris or of lichen pilaris sans spinosus. On purely morphologic dermatologic grounds this is more like lichen spinulosus than pityriasis rubra pilaris.

DR. DOUGLAS TORRE: I agree with the previous speakers. This patient has shown some patchy erythematous lesions from time to time, but the picture presented today, showing definite spines, would fit more in the diagnosis of lichen spinulosus.

Hypertrophic Lichen Planus. Presented by DR. ALEXANDER W. YOUNG JR.

From: The New York Hospital.

Duration: Three years.

Site: Anterior portion of the legs.

History: The patient is a 69-year-old woman, a schoolteacher. She has been presented before the Academy upon two previous occasions with a diagnosis of hypertrophic lichen planus.

Her condition began in 1951 as a generalized multiform erythema (negative drug history). Later, in 1954, when the patient returned for further treatment, she presented a typical lichen planus involving the mouth, extremities, and body. With conservative management, this improved. However, a residual hyperkeratotic dermatitis has remained on the legs.

In April, 1957, the patient presented herself for treatment. A course of applications of thorium X was prescribed for the leg condition: 10 applications (150 mc. in alcohol) to the right leg, 8 to the left.

Examination shows a flat violaceous-to-pink confluent dermatitis on the anterior portions of both legs. This is in marked contrast to the raised hyperkeratotic condition of six months ago.

Laboratory studies, including numerous and repeated blood cell counts and urine examinations, have been within normal limits.

Findings on biopsy show that the epidermis is regularly acanthotic and covered by a thickened, densely laminated horny layer. The granular layer is thickened or increased. There is a moderate, simple cellular, diffuse reaction in the upper cutis. The vessels are dilated; some contain blood cellular elements.

Diagnosis: Lichen planus (hypertrophic).

Discussion

DR. VICTOR H. WITTEN: If I am not mistaken, Dr. Schweich has presented cases with small lesions of hypertrophic lichen planus treated with

thorium X before this Section. There are reports in the literature of this type of lichen planus being treated successfully by this modality. One should qualify the words "treated successfully" or use, for example, "treated to advantage" and "benefited by" thorium X. This is a case in point, as for this patient thorium X is really the first modality that has given her any real comfort from the amount of itching that she has had. It would be interesting to hear something of the schedule that has been used in the treatment of this particular patient.

DR. HARRY J. KATZ: Some time ago I treated a similar case with thorium X, and the patient benefited quite a bit. The scaling and thickening disappeared, and the pruritus subsided. Unfortunately, a few months after treatment was stopped the entire condition recurred. I just wonder how permanent the effect of thorium X would be in this case.

DR. ALEXANDER YOUNG JR.: I have treated this patient with repeated applications of thorium X over the last eight months. She has had 10 applications to the right leg and 8 to the left. Thorium X in alcoholic solution, 150 mc. per cubic centimeter was used. The result, although not dramatic, has been eminently satisfactory. It is my intention now to observe these lesions for possible recurrence without further treatment.

I might close by saying that this patient is quite an enthusiast of the Academy. This is her third presentation, and I am sure she will be overjoyed to return in a year to show the result of her care.

Case for Diagnosis. Presented by DR. ALEXANDER W. YOUNG JR.

From: The New York Hospital.

Duration: Three years.

Sites: Elbows, dorsa of the hands, face, groin, intragluteal region, knees, feet.

History: The patient is a 41-year-old white man, a presser. His dermatitis began three years ago as a discrete, vesicular exudative dermatitis involving the elbows. Subsequently spread has occurred, with remissions and exacerbations of the condition; however, the patient has never been entirely free of the disorder. Pruritus is severe. Consultation and treatment elsewhere, which have included cortisone and tests for food allergens showing reaction with ice cream, lemons, fish, and watermelon (according to the patient), have been unrewarding. The patient has found some relief on his own by using starch baths.

Past and medical histories are essentially negative. The patient's son suffers from atopic dermatitis. Physical examination is entirely negative.

Examination shows the dermatitis to be composed of single, grouped, and confluent papular lichenified lesions. An occasional excoriation and, until recently, single vesicular lesions upon an erythematous base are seen.

Laboratory examination shows CBC within normal limits; urine, negative; S. T. S., negative; sedimentation rate, 31 mm. in an hour; chest film, negative; C. M. I., high number of yes answers.

Findings on biopsy show the vessels of the mid- and upper cutis dilated and the walls thickened. About them is a focal, simple cellular infiltrate with an occasional eosinophil. There is moderate interstitial edema. Within the epidermis is a vesicle containing polymorphonuclear cells, eosinophils, and debris. The basal-cell layer is disturbed. In other sections the epidermis is regularly acanthotic.

Diagnosis: Neurodermatitic reaction.

Course: Over the last two weeks high doses of vitamin A have been used. An antipruritic ointment and starch baths have been prescribed. Improvement has been marked.

Discussion

DR. MAURICE J. COSTELLO: The pruritic papulovesicles on the scalp, face, elbows, knees, and nates speak for dermatitis herpetiformis.

DR. DAVID BLOOM: The location, the scarring, and the pigmentation are typical of dermatitis herpetiformis.

DR. MAURICE J. COSTELLO: One point I should like to add is that this patient should be treated with Promacetin, which is the drug of choice in the treatment of this disease. It is also less toxic, but oftentimes a cure is not forthcoming because the dose should be increased above the usual 3 gm., even as high as 6 gm. a day. You may fail with a dose of 3 gm. and cause remission and complete involution of the lesions with 6 gm. of Promacetin daily.

DR. EDWARD H. MANDEL: I should like to suggest that if Promacetin is used great caution be exercised in observing the patient, as severe secondary anemia may develop. I have seen several patients that almost died after taking Promacetin.

DR. VICTOR H. WITTEN: I want to ask Dr. Costello if he used the word "cure" to mean just that?

DR. MAURICE J. COSTELLO: The word was used loosely. I meant that the disease would be controlled by Promacetin.

DR. ANTHONY CIPOLLARO: Mr. Chairman, the question of cure came up in connection with Duhring's disease. Is it the impression of the members here that Duhring's disease is never cured? My experience leads me to the conclusion that Duhring's disease is sometimes cured with various types of therapy.

DR. PAUL GROSS: I agree with Dr. Cipollaro, but I think that one of the important features of therapy of Duhring's disease is the dosage of time.

DR. JACK WOLF: If it is the dosage of time then it cannot be the active therapy. It cannot be both. It has to be one or the other.

DR. VICTOR H. WITTEN: I was going to comment in a way similar to the comment by Dr. Gross. The action of the sulfones in the management of dermatitis herpetiformis probably is not comparable to the use of steroids in treating pemphigus, a heretofore fatal disease. The continued and proper use of corticosteroids and corticotropin in patients with pemphigus apparently keeps them alive through an otherwise usually fatal disease. In dermatitis herpetiformis, with the proper medications, the patient is kept comfortable so that life is worth living until he outgrows the disease, which he would probably do without therapy. How often do we see elderly patients continuing to be troubled with dermatitis herpetiformis over the years and eventually dying with the disease? Such an incidence must be very low indeed, thus indicating that the majority do get over their dermatitis herpetiformis as the result of the natural course of the disease.

DR. JACK WOLF: I presume that that brings up many questions, including the frequency with which the diagnosis of dermatitis herpetiformis is made and how often that diagnosis is warranted. Everybody will agree that we are dealing here with dermatitis herpetiformis. The many questions raised, however, cannot be answered in the available time.

DR. MAURICE J. COSTELLO: There is only one thing I want to say. I sent this question to all the members of the American Dermatologic Association one time, and the consensus was that about 12% of the patients were cured. I have had a patient who had Duhring's disease for 30 years. I think that in the great majority the condition does not clear up, at least in a relatively short period time. Finally the disease wears itself out. It may remain for decades if not controlled with the sulfonamides.

Poikiloderma of Civatte. Presented by DR. ORLANDO CANIZARES for DR. E. P. NORRIS.

Lichen Planus with Bullae. Presented by DR. ORLANDO CANIZARES for DR. R. SILVES.

Necrobiosis Lipoidica. Presented by DR. ANTHONY CIPOLLARO.

Linear Scleroderma. Presented by DR. ANTHONY CIPOLLARO for DR. MARK MARCIANO.

Pityriasis Rosea. Presented by DR. THOMAS GRAHAM for DR. HERBERT SPOOR.

Generalized Lichen Planus. Presented by DR. HARRY J. KATZ for DR. ROBERT ABEL.

Epidermolysis Bullosa. Presented by DR. HARRY J. KATZ for DR. MARK MARCIANO.

Contact Dermatitis Due to Duplicating Paper. Presented by DR. CHARLES SHEARD.

Linear Nevus. Presented by DR. CHARLES SHEARD for DR. MARK MARCIANO.

Shoe Dermatitis; Nickel Sensitivity; Unsatisfactory Response to "Metal Neutralizer" Barrier Cream. Presented by DR. CHARLES SHEARD for DR. HERBERT SPOOR.

Discoid Lupus Erythematosus (Telangiectatic Variety Following Treatment. Presented by DR. ALEXANDER W. YOUNG JR.

Ochronosis. Presented by DR. ALEXANDER W. YOUNG for DR. MARK MARCIANO (previously presented May 1, 1956).

Case for Diagnosis: Parapsoriasis en Plaque? Presented by DR. HARRY J. KATZ for DR. WILLIAM ANDERSON.

PHILADELPHIA DERMATOLOGICAL SOCIETY

James M. Flood, M.D., Chairman
Herbert A. Luscombe, M.D., Secretary
Nov. 15, 1957

Porphyria (Congenital? Mixed?). Presented by DR. LOUIS JAFFE and (by invitation) DR. JACOB G. SHADE.

A white boy aged 8, well nourished, well developed, and hairy for his age, presented shallow punched-out irregular scars over the chin, cheeks, left ear, and nape and crusted ulcers and scars over the knuckles, chiefly the metacarpophalangeal joints. A 14 mm. thick-walled tense bulla, clear and translucent, was present on the radial side of the right index finger; a 4 mm. bulla, on the dorsal surface of the base of the right thumb, and another, on the extensor surface of the left elbow. The distal two-thirds of the thumbnails were discolored brownish-purple. The knees were spared.

The patient had a "cold" in September, 1956, and received an injection for it. Shortly thereafter the mother noted pink urine off and on, especially in the morning. A month later the patient had swelling of the left elbow and fever. He received penicillin, acetylsalicylic acid (aspirin), and sulfonamides for rheumatic fever. The mother feels certain that she noticed red urine shortly after the patient first began to take sulfonamides. During the second week in May, blisters appeared on the hands. These were ruptured by the mother, producing "sores."

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The patient's paternal aunt has asthma, and his mother has undiagnosed abdominal pains, thought to be from the gallbladder. He has no brothers or sisters.

The liver and spleen are not palpable.

Urinalyses were not remarkable except for reddish color; various specimens fluoresced with orange and, at times, bright-pink fluorescence. A 24-hour urinalysis for porphyrins revealed (1) trace quantities of porphobilinogen, (2) uroporphyrin in greater quantity than coproporphyrin, and (3) uroporphyrin consisting principally of Uroporphyrin III. The mother's urine failed to fluoresce abnormally; the father's urine also failed so to fluoresce. The patient's urine continued to fluoresce with undiminished intensity more than two months after cessation of sulfonamides. A complete blood count revealed 12.5 gm. hemoglobin, 43% hematocrit, 4150 leukocytes, 63% segmented cells, and 37% lymphocytes.

The report on the biopsy specimen was as follows: "This specimen of skin showed a subepidermal bulla. The epidermis was raised clearly off the corium and the resulting space contained some inflammatory cells (a few polymorphonuclear leukocytes and some lymphocytes) and some serous debris. There was a mild inflammatory infiltrate scattered in the dermis. These findings would fit in with porphyria as well as epidermolysis bullosa. Elastic tissue stain showed normal elastic tissue."

The patient was treated with avoidance of sulfonamides, barbiturates, Terramycin, alcohol, and other hepatotoxic drugs, and avoidance of strong sunlight, heat, trauma, and artificial ultraviolet light was recommended. A-Fil was used locally. Secondary infection was controlled with neomycin, bacitracin, polymyxin ointment. Bulla formation decreased markedly, and most scars have become shallow and cosmetically much less objectionable with the passage of time. New bullae have become a rarity.

Discussion

DR. THOMAS PASTRAS (Collingswood, N. J., by invitation): The disease entity porphyria is divided into two major lesions, congenital or erythropoietic and hepatic. If this child's disease is classified as the erythropoietic type, he must have systemic disease involving particularly the bone marrow and more specifically the red cell series. Clinically these cases have red teeth and perhaps hematuria, in addition to hirsutism and bulla formation. Laboratory studies show uroporphyrin Type 1 and no porphobilinogen. My impression is that this child has a polymorphous light eruption with porphyrinuria triggered by sulfonamide therapy.

DR. LOUIS JAFFE: I should regard the sulfonamides as unlikely causes, because none have been given since May. It is unlikely to be anything other than porphyria. The red teeth are seen only in deciduous teeth. The patient has a few features of the acute intermittent and also some of the congenital type. I do not think we should ignore these in order to fit him into one of our pigeonholes.

DR. ALBERT M. KLIGMAN: I do not think that this is simply a case of comforting ourselves with putting it into a pigeonhole. These diseases are as different as they can be. There are distinctive means, simple means, of distinguishing them. In this case, if we had a bone marrow sample we could tell in five seconds whether he had erythropoietic porphyria. It seems to me that the picture is more characteristic of this, though far from classical. This is a pretty marked blistering eruption. Blistering of this degree is not characteristic of the cutanea tarda or chronic intermittent type. These people do not have marked photosensitivity; they get dermatitis which eventually ends like radiodermatitis. They have hyperpigmentation and hairiness; the age group is older in this case. Hepatic porphyria is inherited as a dominant; erythropoietic porphyria, as a recessive. Neither parent had uroporphyrins. Incidentally, it looks to me as if development has been somewhat impaired in this child; he has not the stature and the physical strength he should have. This is a serious disease, and I feel that this is more consistent with the congenital type of porphyria. Perhaps the older clinicians would have called this hydroa vacciniforme.

DR. LOUIS JAFFE: The type of porphyrins found in the analysis are those which fall into the hepatic type of porphyria, and the erythrocytic type does not usually have its onset following the ingestion of sulfonamide, and so we have to protect the boy against both hepatotoxic factors and undue exposure to irradiation.

DR. GEORGE B. HAMBRICK JR.: If this is congenital, why did it take so long to develop? Most people manifest it earlier than this child has. I think the sulfonamides triggered this boy's disease. You can argue about it until you are tired, but there are certain features here of porphyria as well as of epidermolysis bullosa. This boy produces blisters by trauma as well as by sunlight. This does fit into the hepatic type of porphyria. I agree that this was triggered by sulfonamides. The boy had liver damage, and he has porphyria of an epidermolysis bullosa type.

Lupus Vulgaris Erythematoides (Leloir). Presented by CAPT. J. H. LOCKWOOD (MC), U. S. N.

A white woman aged 79, somewhat asthenic, in no acute distress, when first seen presented multiple large erythematous discoid lesions over the chin, cheeks, forehead, and ears. The margins of

the lesions were raised and erythematous. Centrally there were atrophy and telangiectases. There was little evidence of follicular plugging except in the ears. Atrophic areas were noted on the scalp.

The patient was seen on Feb. 1, 1950, at the Barnes Hospital in St. Louis, because of an erythematous eruption of the face of about one year's duration. Clinically, she was thought to have discoid lupus erythematosus, but the findings on biopsy were compatible with sarcoid. She was treated with potassium arsenite solution (Fowler's solution), Moogrol, ultraviolet light, Bistrimate, and isoniazid, with clearing. She did well until early 1957, when recurrence was noted. She was seen at Barnes Hospital in January, 1957, when findings on a repeat biopsy were said to be suggestive of sarcoid. She was treated with Inh, and the condition cleared. Since July, 1957, there has been progressive reappearance of the lesions. She was seen at the Naval Hospital in Philadelphia during September, 1957, with the foregoing history.

The patch test for tuberculosis was positive. A complete blood cell count was within normal limits. The serologic tests for syphilis were negative. A roentgenogram of the chest showed evidence of an old calcified primary complex.

Reports on biopsy specimens were as follows: Barnes Hospital, 1950: compatible with sarcoid; Barnes Hospital, 1957: suggestive of sarcoid; United States Naval Hospital, Philadelphia, 1957: suggestive of lupus vulgaris.

The patient has been treated with 250 mg. of chloroquine every other day, with good response.

Discussion

CAPT. J. H. LOCKWOOD (MC), U. S. N.: When we first saw this patient, we thought that the condition was lupus erythematosus. Biopsies were done in 1950 and 1957, and each was thought to be sarcoid. Thinking she had lupus erythematosus, we started therapy with chloroquine and, strangely enough, she did improve while taking chloroquine. On looking at the slide, Dr. Beerman suggested lupus vulgaris, and we looked into the matter more closely. Clinically this case seems to fit into the picture of lupus vulgaris of the erythematous telangiectatic type of Leloir. Histologically we have reviewed the slides from the Barnes Clinic, and they do show a great number of giant cells, more than one would expect in sarcoid; there are areas which show necrobiosis almost to the extent of caseation; the areas of involvement in the dermis are close to the epidermis. There is a possibility, of course, that this could also be the erythematous type of sarcoid, but in our opinion the histologic picture favors lupus vulgaris rather than sarcoid in the three sections that have been taken, two at St. Louis and one here. We expect to change the treatment to isoniazid. She had isoniazid for about a month in St. Louis, with good results, and we are going to give it another try.

DR. DOUGLASS A. DECKER (Allentown, Pa.): Isn't she, rather old to develop lupus vulgaris?

CAPT. J. H. LOCKWOOD (MC), U. S. N.: She is rather old to develop lupus vulgaris, but it has been seen in even older patients.

Keratoacanthoma. Presented by CAPT. J. H. LOCKWOOD (MC), U. S. N.

A white man aged 24, with no apparent systemic illness, presented a 2 cm. granulomatous nodule on the tip of the nose with a central area of ulceration covered by a dry serous crust. The edges of the lesion were rather firm. There was no significant lymphadenopathy. There was onset of a scaling eruption on the nose approximately six to eight months ago which became papular and slightly tender in August, 1957. A biopsy was made at that time, and findings were reported to the patient as benign. The lesion was treated by electrofulguration on Sept. 26. Since that time there has been persistent ulceration with gradual enlargement of the tumorous growth on the tip of the nose.

A complete blood cell count revealed 15.6 gm. hemoglobin, 6550 leukocytes, 48% neutrophils, 50% lymphocytes, and 2% eosinophils. The urinalysis was within normal limits. Culture from the ulceration grew out a hemolytic Staphylococcus pyogenes var. aureus sensitive to penicillin, erythromycin, Aureomycin, and Cathomycin. VDRL was negative. Roentgenograms of the chest, paranasal sinuses, and nasal bones were all within normal limits.

The report on the biopsy specimen on Nov. 8, 1957, was consistent with keratoacanthoma.

No specific treatment other than the biopsy of the lesion on Nov. 8, 1957, has been administered.

Figure 1

Figure 2

Discussion

CAPT. J. H. LOCKWOOD (MC), U. S. N.: This lesion has been present for only about a month to six weeks. There had been a dry scaling area on the nose previous to that. The histopathologic picture from the one biopsy is suggestive of keratoacanthoma. There was marked hyperkeratosis with marked pseudoepitheliomatous hyperplasia, with very little tendency toward dyskeratosis among the epidermal cells. The corium showed increased vascularity to the extent of telangiectasia. He also gives a history of having a bluish lesion present before it was fulgurated. This accounts to some extent, I think, for the ulcerating appearance of the center of the lesion. There is still the serious question of whether this man may have a squamous-cell epithelioma. We want another biopsy specimen from the opposite side of the lesion and deeper cuts into site of the biopsy specimen we already have to see whether we can find other changes. This might have been a pyogenic granuloma (history of blue nodular lesion) which has sclerosed down, with the production of pseudoepitheliomatous hyperplasia. It is not the exact picture one expects to find in a keratoacanthoma. Should this be completely removed by surgery and a graft applied, or should we try some superficial roentgen-ray therapy to control the inflammatory element? We are awaiting future biopsies. I should appreciate any suggestions.

DR. ALBERT M. KLIGMAN: I think that the family history is contributory. This man's father died of squamous-cell carcinoma of the face at an early age. This may be something we should consider. It is a little early for a keratoacanthoma, although it is in the right place. One can never be 100% sure of the diagnosis of keratoacanthoma. It may be squamous, although the histopathology does not suggest that. This reminds me of that patient we had at the University. He began with a lesion very similar to this one; first a lesion like a basal-cell carcinoma—a furunculoid type of lesion on the face—spread to the nose, and no matter what was done to it it spread, eroded, and dissected down to the deep tissues and became a phagedenic ulcer. We could not stop it by antibiotic therapy, and that man died. I think that there is just enough doubt here to wonder whether we are not faced with whatever this spreading type of phagedenic ulcer is.

DR. MILTON M. CAHN: You can make a diagnosis of keratoacanthoma only in a typical case. This is not a typical case. You have to think of squamous-cell epithelioma, and I think that Dr. Beerman will bear me out in saying that the histopathologist cannot make a diagnosis of keratoacanthoma per se.

DR. HERMAN BEERMAN: I understand that at Temple University they can make an objective histologic diagnosis of keratoacanthoma. I cannot do this with certainty.

DR. MARGARET GRAY WOOD: Dr. Kligman has referred to a patient presented to the Philadelphia Dermatological Society on Feb. 15, 1957 (A. M. A. ARCH. DERMAT. 76:675-676, 1957). Two biopsy specimens, presented to me with the clinical diagnosis of tertiary gummatous syphilis, showed granulomatous changes compatible with this diagnosis. However, the subsequent downhill clinical course, with fatal outcome, along with negative serologic tests for syphilis, indicated that the correct diagnosis was that of malignant granuloma of the midline facial tissues. The lesion was histologically a granuloma and bore no resemblance to the primary epithelial (squamous-cell-type) hyperplasia demonstrated by the lesion presented tonight.

DR. JAMES M. FLOOD (Sayre, Pa.): I saw a case similar to this in an elderly man; biopsy had been performed in Binghamton, N. Y., on two occasions, and a diagnosis of keratotic lesion had been made. When I saw it, it looked like squamous-cell carcinoma, but I waited a few weeks more to see whether it would heal. It gradually progressed. We did another biopsy, and this time a diagnosis of squamous-cell carcinoma was made. Repeat biopsy proved this lesion to be squamous-cell carcinoma.

Pityriasis Lichenoides Chronica of Juliusberg. Presented by DR. JOHN P. SCULLY (Reading, Pa.).

A white boy aged 10 on Oct. 14, 1957, first presented a few "red spots" on the abdomen which looked to the mother like measles. He had had a runny nose all week with no fever or malaise, although another child in the house, along with the mother, developed the typical symptoms of the

influenza infection that was rampant in the neighborhood. The child's rash kept spreading, appearing on the face 72 hours later and then on the arms and the upper thighs. There was little or no itching and no burning.

On the evening of Oct. 17, 1957, the patient developed fever, and by the next day the temperature went up to 103 F and the rash was much more prominent.

There was a history of a "flu shot" on Oct. 16, 1957. The patient had been getting no medication prior to the onset of the eruption. There was a past medical history of German measles at 4 years of age. He had nosebleeds frequently as a younger child.

Physical examination on Oct. 19, 1957, showed a profuse erythematous excoriated and slightly crusted papular eruption most marked over the trunk, with scattered lesions over the arms, forearms, and upper [illegible] with a few lesions on the face; there was no evidence of old plaque. The papules measured, for the most part, 4 to 6 cm. in diameter and initially were bright red. There was moderate lymph node enlargement of the cervical glands and moderate bulbar conjunctival infection. No abdominal organs were palpable. The chest was clear. The patient continued to have fever for the next 24 hours, with temperature reported normal on Oct. 21, 1957. However, new lesions kept appearing on the extremities. The child had a slight cough on Oct. 21, 1957. The tourniquet test was negative for increased capillary fragility. The lesions were a livid red at this time and varied from pinpoint to 3 to 6 mm. in size.

The child has remained afebrile. The lesions have become less florid with more evidence of scale and persistence of the papular characteristics.

The report on the biopsy (Nov. 11, 1957) was chronic dermatitis.

Discussion

CAPT. J. H. LOCKWOOD (MC), U. S. N.: Another case we had resembled more the Mucha-Habermann type, with some lesions suggestive of the Juliusberg type. Ingram, of Leeds, England, feels that these children do develop a type of parapsoriasis that seems to be more of a cross between the Mucha-Habermann and the Juliusberg types, having a much more favorable prognosis. I think that this is important as far as giving information to the patient's parents is concerned.

DR. ALBERT M. KLIGMAN: Since this came on so suddenly and does not appear to be the Mucha-Habermann type, could this be an atypical pityriasis rosea? This condition seems to be diminishing somewhat. It did come on after some sort of febrile episode, and I do not know how you can make a diagnosis of parapsoriasis unless you wait for several months and find out that it does not go away.

DR. GEORGE B. HAMBRICK JR.: I should not be so optimistic about the prognosis, so far as getting rid of the eruption is concerned. I think that in Ingram's cases it would be years before remission occurred. I think that you can say that this type of parapsoriasis does not eventuate in lymphoblastoma, as the other types so often do.

DR. JOHN P. SCULLY (Reading, Pa.): I am interested to hear it said that this does not eventuate in lymphoblastoma because I am completely confused, now, about this business of parapsoriasis. I have a patient, a 43-year-old male school teacher, diagnosed 20 years ago by Guy Lane as having parapsoriasis en plaque. He had no other symptoms, but Dr. Wood, to whom I showed a slide the other day, said it was a beginning lymphoma.

DR. GEORGE G. HAMBRICK JR.: Dr. Ingram makes a distinction between parapsoriasis guttata and parapsoriasis of Juliusberg; parapsoriasis guttata is a more psoriasiform type of lesion that does not come and go but persists in the same sites, whereas in pityriasis of Juliusberg the eruption goes through a definite course, ending as a somewhat depigmented scaly lesion. Some of these cases in adults have eventuated in lymphoma, but I do not believe any of the childhood cases have.

Parapsoriasis, Retiform Type. Presented by DR. HAROLD L. COLBURN, Camden, N. J.

Lichen Sclerosus et Atrophicus. Presented by DR. HAROLD L. COLBURN, Camden, N. J.

Granuloma Annulare. Presented by DR. HERBERT A. LUSCOMBE and DR. JOSEPH K. CORSON.

Pemphigus Vulgaris of the Mouth, Conjunctiva, and Anus. Presented by DR. JOSEPH K. CORSON.

Psoriasis of Face, Arms, and Legs. Presented by DR. HERBERT A. LUSCOMBE.

Psoriasis of the Nails. Presented by DR. MARGARET G. MAHONEY.

Sarcoidosis. Presented by DR. HERBERT A. LUSCOMBE.

Linear Lichen Planus. Presented by DR. HERBERT A. LUSCOMBE and DR. HAROLD L. COLBURN, Camden, N. J.

Necrobiosis Lipoidica. Presented by DR. JOSEPH K. CORSON.

Pseudopelade. Presented by DR. JOHN P. SCULLY, Reading, Pa.

Abstracts from Current Literature

EFFECTS OF BACTERIAL ENDOTOXINS ON SUSCEPTIBILITY TO INFECTION WITH GRAM-POSITIVE AND ACID-FAST BACTERIA. R. J. DUBOS, R. W. SCHAEDLER, and D. BÖHME, Fed. Proc. 16:856-857 (Sept.) 1957.

Injection into experimental animals of sublethal doses of bacterial endotoxins (lipopolysaccharides) first depresses and later increases resistance to infection with Gram-negative bacilli unrelated to the strain from which the endotoxin was prepared. This biphasic nonspecific effect on resistance has been found to apply also to infection with Gram-positive and acid-fast organisms. It can be elicited by injection of killed tubercle bacilli, pertussis vaccine, or extracts of these organisms. A chronic infection produced by sublethal doses of staphylococcal or mycobacterial organisms can be converted months later by injection of lipopolysaccharide into an acute process, the explosive multiplication of the bacteria often resulting in the death of the animal. In contrast, administration of similar doses or less of bacterial products injected into uninfected animals resulted in an increase in their resistance to subsequent infection with various types of pathogens.

MONASH, Miami, Fla.

HOST RESPONSES ELICITED BY POLYSACCHARIDES OF BACTERIAL AND MAMMALIAN DERIVATION. M. LANDY and M. J. SHEAR, Fed. Proc. 16:857-860 (Sept.) 1957.

Until now it has been thought that only lipopolysaccharides derived from bacterial sources are capable of altering resistance to infection and serum properdin levels in mice or of producing hemorrhage and necrosis in sarcomas in man and animals, leukocytic changes, and fever. The authors have found that these effects can also be produced by polysaccharides derived from many animal and plant sources, such as mouse kidney, lung, liver, and stomach; mouse sarcoma and carcinoma; rabbit skin; chick embryo skin; tangerine; bryonia root; Serratia marcescens, and Salmonella typhosa. Polysaccharides derived from one species will produce these effects when injected into animals of the same species. This suggsts that polysaccharides present in the tissues and released into the circulation may play a part in resistance, infection, and shock.

MONASH, Miami, Fla.

THE STUDY OF THE EFFECT OF CERTAIN CHEMICALS ON PERSPIRATION FLOW. G. F. COLLINS and J. E. CHRISTIAN, J. Am. Pharm. A. (Scient. Ed.) 47:25-29 (Jan.) 1958.

A number of new antiperspirant salts were prepared and tested on the thoracic surface of the horse for their effect on apocrine gland perspiration. On a molar basis, the most effective salt was lanthanum sulfamate, followed in diminishing order by lanthanum methionate, cerous methionate, cerous sulfamate, lanthanum chloride, aluminum chloride, zinc methionate, aluminum methan sulfonate, and aluminum sulfate. Other chemically related metals of the lanthanide series of the periodic table, namely, praseodymium, neodymium, samarium, europium, yttrium, and scandium, should also show antiperspirant action.

MONASH, Miami, Fla.

GLYCOLYTIC AND RESPIRATORY ENZYMES OF TRICHOPHYTON MENTAGROPHYTES. E. M. JENSEN, H. ALTSCHULLER, and R. C. BARD, J. Bact. 74:656-660 (Nov.) 1957.

Studies of the enzymatic activity of cell-free extracts of Trichophyton mentagrophytes indicate the presence of both the hexosediphosphate and hexosemonophosphate pathways of carbohydrate dissimilation as well as the tricarboxylic acid cycle. Coenzyme specificity for the dehydrogenases has been demonstrated. With the exception of 3-phosphoglyceraldehyde dehydrogenase and one of the two glycerol dehydrogenases, all show a specific requirement for triphosphopyridine nucleotide.

BLANK, Miami, Fla.

SCABIES AND THE QUEEN MAB PASSAGE IN ROMEO AND JULIET. HARRY KEIL, J. Hist. Ideas 18:394-410 (June) 1957.

In an intriguing paper with a depth of classical scholarship rarely enrountered, the author makes a good case for his thesis that the Acarus scabiei was known in Shakespeare's time.

He points out that although Renucci, in 1834, was the first to show scientifically that this parasite was the cause of human scabies, the technique for demonstrating the parasite was based on information widely known among the lay people in Corsica, Renucci's native land. The passage from "Romeo and Juliet," written in 1595, that Keil believes refers to the scabies mite is as follows:

> Her waggoner, a small grey-coated gnat,
> Not half so big as a round little worm
> Prick'd from the lazy finger of a maid.

BLANK, Miami, Fla.

TREATMENT OF CHILBLAINS BY PHENOXYBENZAMINE. SOUTH-EAST SCOTLAND FACULTY OF THE COLLEGE OF GENERAL PRACTITIONERS, Brit. M. J. 2:1521 (Dec. 28) 1957.

A "double blind" study was conducted in order to determine the therapeutic value of phenoxybenzamine in the treatment of chilblains. In the 103 cases analyzed there was a significant beneficial effect from the drug. The action of the drug is to oppose the vasoconstrictor action of the sympathetic nervous system. The dose was from 1 to 3 capsules (10 mg. each) per day. There were significant undesirable side-effects, including nasal congestion, dry mouth, dizziness, tachycardia, and swollen eyelids.

NORINS, Chicago.

THE ENANTHEM OF GLANDULAR FEVER. F. CAIRD and P. HOLT, Brit. M. J. 1:85 (Jan. 11) 1958.

Palate lesions were found in 45 patients out of a group of over 200 with an acute febrile illness in whom glandular fever (infectious mononucleosis) was a diagnostic possibility. Of this group, 28 were proved to have glandular fever. The most characteristic eruption consisted of multiple pin-point petechiae on the palate. This finding, in the absence of petechiae elsewhere, is strong clinical evidence of glandular fever (if rubella can be excluded). The duration of the lesions coincided with the duration of the fever.

NORINS, Chicago.

PORPHYRIA. GEOFFREY DEAN and H. BARNES, Brit. M. J. 1:298 (Feb. 28) 1958.

The authors classify porphyria according to three genetic types: porphyria erythropoietica, the Swedish type of porphyria hepatica, and the South African type of porphyria hepatica. The South African type is characterized by acute attacks occurring most commonly in women and precipitated by drugs. Light sensitivity is usually found in men but not in women with the disease. The latent phase of this type of porphyria can often be detected by screening procedures including a simple fecal test, which the authors describe. In screening 1253 South African whites, 15 cases of porphyria were found.

NORINS, Chicago.

FUNGISTATIC ACTIVITY OF SOME HYDROXAMIC ACIDS. J. ALKIEWICZ, Z. ECKSTEIN, H. HALWEG, P. KRAKOWKA, and T. URBANSKI, Nature, London 180:1204-1205 (Nov. 30) 1957.

Salicylhydroxamic acid is active in vitro against pathogenic dermatophytes. The authors treated 21 cases of superficial fungus infections with this drug given by mouth for 10 days in doses of 1 gm. to adults and 0.5 gm. to children daily. They report spectacular healing of lesions, without toxicity. Additional chlor-derivatives of the compound have been prepared which are more active in vitro.

BLANK, Miami, Fla.

DETERMINATION OF THE LEVELS OF ANTISTREPTOLYSIN O AND ANTISTAPHYLOLYSIN IN THE SERUM OF PATIENTS WITH VARIOUS DERMATOSES, C. HURIEZ, F. DESMONS, and J. BAELDEN, Ann. dermat. et syph. 85:5-25 (Jan.-Feb.) 1958.

From a study of 200 patients it was learned that the antistreptolysin O is low in the course of lupus erythematosus, lichen planus, and Duhring's disease; that it is elevated in 21% of patients with eczema and 30% of those with leg ulcers, and that it is particularly elevated in infantile pyodermas (43%), in nodular nonvascular hypodermites of adults (42%), in erythema multiforme, and in erythrodermic psoriasis (50%). The values of the antistaphylolysins were normal except in suppurative staphylococcal dermatoses of long

duration (furunculosis, in particular). The chief value of the study was the demonstration of the important role of the Streptococcus in conditions in which it is not evident clinically.

DERBES, New Orleans.

ACQUIRED ICHTHYOSIS AND HODGKIN'S DISEASE. Y. BUREAU, R. PICARD, and H. BARRIÈRE, Ann. dermat. et syph. 85:30-40 (Jan.-Feb.) 1958.

Acquired ichthyosis has been reported as a manifestation of malignant disease of the reticuloendothelial system (Hodgkin's disease, mycosis fungoides, lymphosarcoma, and reticulosarcoma) and in one case of metatastic carcinoma of the breast. The author's case is added to the 15 others reported since 1943.

DERBES, New Orleans.

A CASE OF MIXED TERTIARY SYPHILIS (TUBERCULOUS AND ULCEROGUMMATOUS), REALLY TARDIVE. K. MASURE and G. BROCHEN, Ann. dermat. et syph. 85:45-47 (Jan.-Feb.) 1958.

The authors describe a case of florid tertiary syphilis which appeared 63 years after a mixed chancre, and was accompanied by a silent aneurysm of the brachiocephalic trunk with perfect conservation of general health and total integrity of the nervous system, the heart, and the aorta in a man 81 years of age.

DERBES, New Orleans.

GROWTH OF CANDIDA ALBICANS ON KERATIN AS SOLE SOURCE OF NITROGEN. L. KAPICA and F. BLANK, Dermatologica 115:81-105 (Aug.) 1957.

Candida albicans can utilize keratin of hoof and nail if 2% to 8% of glucose is present in the media. Nitrogenous break-down products were determined over a period of four months, and it is concluded that C. albicans can digest keratin.

PINKUS, Monroe, Mich.

ELASTICITY OF HUMAN SKIN RELATED TO AGE. L. H. JANSEN and B. B. ROTTIER, Dermatologica 115:106-111 (Aug.) 1957.

Strips of abdominal skin 10 cm. long and 0.5 cm. wide were obtained from cadavers and a few surgical patients and were stretched with weights ranging from 10 to 300 gm. This corresponds to a maximum load of 33 gm. per square millimeter. At these "physiological" loads there were no significant differences of extensibility at different ages. Individual variation was considerable.

PINKUS, Monroe, Mich.

THE DIFFERENTIAL DIAGNOSIS BETWEEN EPIDERMOLYSIS BULLOSA HEREDITARIA AND PORPHYRIA CUTANEA TARDA. T. T. HOO, Dermatologica 115:112-119 (Aug.) 1957.

After a general review of clinical differences in which stress is placed on differences in localization without the addition of much that is new, the author reports on determinations of porphyrins in urine and feces of six patients afflicted with epidermolysis bullosa. No connection between porphyrin metabolism and this disease was found.

PINKUS, Monroe, Mich.

LOCALIZED CURLY-HAIR NEVI IN SMOOTH CAPILLITIUM. W. BORN, Dermatologica 115:119-121 (Aug.) 1957.

An 8-year-old boy with smooth blond hair had persistent growth of tightly curled hair in an area several centimeters in diameter. The scalp showed no visible changes when the hair was shaved off. Only a few similar cases have been reported in the world literature.

PINKUS, Monroe, Mich.

EXPERIENCES WITH SUPERSONIC WAVES IN DERMATOLOGY. F. MAAG, Dermatologica 115: 121-135 (Aug.) 1957.

After treating 217 patients with leg ulcers, x-ray ulcers, acne vulgaris, warts, and clavi, the author concludes that supersonic waves have little practical value except in the treatment of x-ray ulcers.

PINKUS, Monroe, Mich.

C-REACTIVE PROTEIN IN BLOOD SERUM AND BLISTER FLUID IN VARIOUS DERMATOLOGICAL CONDITIONS. R. ROZANSKY and J. SHANON, Dermatologica 115:136-142 (Aug.) 1957.

Tests for C-reactive protein were done on 143 samples of blood and 58 samples of blister fluid obtained from natural bullae or cantharides blisters in a great variety of dermatoses.

Forty-two diagnoses are tabulated. Positive tests were obtained in the acute phase of several conditions and generally paralleled an elevation of the sedimentation rate. The protein practically always was present in blister fluid if it was also present in the blood serum, and it seems to pass from the blood into the bullae.

PINKUS, Monroe, Mich.

NEW DATA ON THE MECHANISM OF ACTION OF ATABRINE. E. NAGY, L. KOCSÁR, I. JÓKAY, C. HADHÁZY, and K. TUZA, Dermatologica 115:143-148 (Aug.) 1957.

On the basis of experimental studies on guinea pigs, cats, and rats the authors conclude that quinacrine (Atabrine) has an antihistaminic action which is not explained by an increase of histaminase in the tissues of treated animals. All animals showed considerable hypertrophy of the adrenal cortex, and it is suggested that increased production of corticosteroids plays a part in the mechanism of the anti-inflammatory effect of quinacrine.

PINKUS, Monroe, Mich.

SOLAR URTICARIA. LOUIS A. BRUNSTING and JOHN H. EPSTEIN, Dermatologica 115:171-180 (Sept.) 1957.

The patient was found sensitive to rays in the short ultraviolet range. Passive transfer was accomplished with his serum. Repeated exposure of the test site reduced the reaction but did not exhaust it. The occlusion of arterial blood from the patient's forearm during a test exposure prevented the abnormal reaction. Treatment with chloroquine increased the threshold of sensitivity.

PINKUS, Monroe, Mich.

ALKALINE PHOSPHATASE IN THE NIPPLE OF THE GUINEA PIG AND ITS RELATION TO THE "NIPPLE TEST." EUGENE BUJARD, Dermatologica 115:181-185 (Sept.) 1957.

The tissues of the nipple of normal male or female guinea pigs do not contain alkaline phosphatase. Pregnant and lactating animals show enzymatic activity in the acanthotic epidermis, in smooth muscle fibers, and in the vascular endothelium. Repeated local application of estrogen to male nipples produces a picture similar to that in the pregnant female. A single application, while causing acanthosis of the epidermis, does not elicit a positive alkaline phosphatase reaction.

PINKUS, Monroe, Mich.

THOUGHTS CONCERNING THE TEACHING OF DERMATOLOGY. W. BUCKHARDT, Dermatologica 115:186-190 (Sept.) 1957.

The author would like to adapt the demonstration of dermatologic patients in separate rooms, as usually practiced at society meetings, to the clinical teaching of medical students.

PINKUS, Monroe, Mich.

TREATMENT OF EPIDERMOPHYTOSIS. C. CARRIÉ and R. BROCKER, Dermatologica 115:190-196 (Sept.) 1957.

A slightly acid liquid of oily consistency containing the butyl esters of carbonic acid mixtures was obtained by treating coal with nitric acid. This product (KT4) was found highly effective in vitro and in the treatment of 150 cases of interdigital dermatophytosis of the feet. It was well tolerated in all stages and did not produce sensitization during the time of observation (about one month).

PINKUS, Monroe, Mich.

THE NOSOLOGIC POSITION OF "OCULAR PEMPHIGUS" (BENIGN MUCOUS MEMBRANE PEMPHIGOID, DERMATITE BULLEUSE MUCOSYNÉCHANTE ET ATROPHIANTE). R. DEGOS, E. LORTAT-JACOB, and P. HARDY, Dermatologica 115:205-217 (Sept.) 1957.

The authors believe that the clinical picture of "ocular pemphigus" may be a part of various bullous dermatoses but is rarely related to true pemphigus vulgaris and infrequently to Duhring's disease. They believe with Lever that there is a clinical entity that may produce symptoms on the eyeball, on other mucous membranes, and on the skin, but they prefer Lortat-Jacob's designation "bullous dermatosis with mucous synechiae and atrophy" to Lever's "benign mucous membrane pemphigoid."

PINKUS, Monroe, Mich.

BAND-LIKE DEGENERATION AND PREDESCEMETIC DYSTROPHY OF THE CORNEA, IN A CASE OF CONGENITAL ICHTHYOSIS. A. FRANCESCHETTI and V. SCHLÄPPI, Dermatologica 115:217-223 (Sept.) 1957.

A unique case combining two different types of corneal abnormality in a 56-year-old man with ichthyosis is presented.

PINKUS, Monroe, Mich.

ATOPIC DERMATITIS (INFANTILE ECZEMA, PRURIGO BESNIER). J. GATÉ, Dermatologica 115: 223-231 (Sept.) 1957.

The author concludes that the designation atopic dermatitis is justified although the process is closely related to allergy. New terms and learned concepts lead us back to the constitutional diathesis of older dermatologists. Treatment of the individual case must consider multiple responsible factors: allergic, dietetic, vascular, and psychosomatic ones.

PINKUS, Monroe, Mich.

LUPUS ERYTHEMATOSUS PROFUNDUS (KAPOSI-IRGANG) AND THE DEEP LESIONS OF LUPUS ERYTHEMATOSUS. J. GAY PRIETO, G. JAQUETI, and A. P. RODRIGUEZ PEREZ, Dermatologica 115:232-247 (Sept.) 1957.

A typical case combining discoid lesions in the skin with subcutaneous nodules is presented. Systematic study of the hypoderm reveals subcutaneous lesions in one out of four cases of discoid lupus erythematosus, according to the authors. These findings argue for the unity of all manifestations of lupus erythematosus. The deep lesions may show sarcoid structure on microscopic examination.

PINKUS, Monroe, Mich.

THE TREATMENT OF LUPUS ERYTHEMATOSUS WITH A COMBINATION OF CHLOROQUINE AND PREDNISONE. A. MIDANA and M. DEPAOLI, Dermatologica 115:677-680 (Nov.) 1957.

Eighteen cases of discoid lupus erythematosus were treated with daily doses of 500 to 600 mg. of chloroquine, together with 10 to 15 mg. of prednisone, resulting in more rapid involution of the lesions than with chloroquine alone.

MONASH, Miami, Fla.

ESOPHAGEAL LESIONS IN PROGRESSIVE SCLERODERMA. J. DELACRÉTAZ and J. PASQUIER, Dermatologica 115:700-705 (Nov.) 1957.

The authors describe several cases of scleroderma which began with Raynaud-like symptoms and gradually extended to involve the esophagus, resulting in stenosis and gastroesophageal disturbances.

MONASH, Miami, Fla.

THE QUESTION OF PERMANENT EPILATION WITH X-RAYS. G. MIESCHER, Dermatologica 115: 706-711 (Nov.) 1957.

Using soft rays (30 kv., beryllium window and 1 mm. aluminum filtration) and fractionation of the dose of 3000 r, by giving daily doses of 200 r. Miescher was able to produce permanent epilation in five cases. Upon being followed for from 1.5 to 4.5 years, one case developed punctate telangiectasis. For this reason the method is not recommended.

MONASH, Miami, Fla.

ERUPTIVE MILIA AND EPITHELIOMA ADENOIDES CYSTICUM. F. MIESCHER, Dermatologica 115:712-716 (Nov.) 1957.

Histologic examination of a case of eruptive milia shows, in agreement with the findings of Epstein and Kligman, that milia develop from epithelial buds. The latter form partly from lanugo follicles and partly from the surface epithelium and probably represent rudimentary sebaceous-gland tissue. This shows the close connection between eruptive milia and epithelioma adenoides cysticum (Brooke's tumor). The two are probably nevoid formations which depend on the same developmental process.

MONASH, Miami, Fla.

RELATIVE THICKNESSES OF TOPICAL MEDICATIONS USUALLY APPLIED TO SKIN. H. IPPEN and H. BETZLER, Arch. klin. u. exper. Dermat. 205:321-330, 1957.

The thicknesses of various topical medications usually applied to the skin was determined by measuring the radioactivity after addition of I^{131}-9,-10,diiodo-oleic acid. The thickness

was not influenced by the area of application. Measured values varied considerably according to the type of application. Frequent values were for petrolatum, 4μ to 10μ; glycerin cream, 9μ to 15μ; an oxycholesterol-petrolatum ointment base (Aquaphor) with water, 2μ to 6μ; liquid petrolatum, 3μ to 6μ, and 10% solution of isopropyl myristinate in isopropyl alcohol, 0.25μ to 1.5μ. The results are considered important for the evaluation of sun preventives.

HOLLANDER, Springfield, Mass.

FORMS OF POIKILODERMA CONGENITALE. P. WODNIANSKY, Arch. klin. u. exper. Dermat. 205: 331-342, 1957.

Poikiloderma congenitale is to be distinguished from poikiloderma of the adult. There are two groups of the congenital form. The first group shows skin changes shortly after birth or during the first years after birth. Thomson's disease and Rothmund's syndrome are to be included in this group. The second group comprises cases in which skin changes already exist at birth. Various ectodermal and mesodermal defects and malformations occur in both groups. Description of a case in a 7-year-old girl which belongs to the second group and is classified as a dominant hereditary disease is presented.

HOLLANDER, Springfield, Mass.

LIVEDO RETICULARIS AND γ-PLASMOCYTOMA CAUSED BY BLOOD GELATION. H. LANGHOF, G. BRAUN, and H. MATZKOWSKI, Arch. klin. u. exper. Dermat. 205:343-350, 1957.

Description of a case of livedo reticularis in a 55-year-old woman with ulcers and hemorrhages of the extremities is presented. Also present was γ-plasmocytoma, with increase of the γ-globulin fraction of the serum. Spontaneous gelation of the blood was already observed at room temperature of 16 C. Myelogram showed 40% reticular plasma cells. The described symptoms of livedo are due to the presence of cryoprotein and cold agglutinins. The cryoprotein originates from plasma cells which were abundantly present in the sternal marrow. The origin of the cold agglutinins could not be determined.

HOLLANDER, Springfield, Mass.

PYO-(RHINO-)STOMATITIS VEGETANS. O. HORNSTEIN, Arch. klin. u. exper. Dermat. 205: 357-372, 1957.

Clinical and histologic description of a case of chronic granulomatous stomatitis and rhinitis in a 56-year-old man is presented. Gastrointestinal symptoms (diarrhea of long duration, duodenal ulcer, inflammatory and hemorrhagic changes of the rectum), inflammatory and degenerative changes of a ganglion of the lumbar sympathicus, marked arteriosclerosis, and pyramidal tract symptoms also existed. The author raises the question of whether this condition, first described by F. McCarthy, in 1949, as pyostomatitis vegetans, is an oligosymptomatic manifestation of pyodermite végétante (Hallopeau).

HOLLANDER, Springfield, Mass.

CORRELATIVE STATISTICS OF OVER 2000 ELECTROPHORESES (ANTWEILER METHOD) IN NEURODERMATITIS BROCQ (ATOPIC ECZEMA) AND OTHER ECZEMAS. C. M. HASSELMANN, Arch. klin. u. exper. Dermat. 205:373-380, 1957.

Evaluation of 2600 blood serum electrophoreses in various dermatoses including over 800 atopic and other eczemas is presented. There was significant decrease of albumin, significant increase of γ-globulin, and questionable increase of β-globulin in atopic eczema. Various forms of eczema showed marked hypoalbuminemia and increase of α-, β-, and γ-globulins. The electrophoretic changes which were found in various forms of eczema are interpreted as hepatic (plasma) syndrome.

HOLLANDER, Springfield, Mass.

SCHÖNLEIN'S PURPURA-LIKE EXANTHEMA WITH UNUSUAL DISTURBANCE OF BLOOD-CLOT RETRACTION. G. W. KORTING, F. K. BELLER, and G. KÖPPEL, Arch. klin. u. exper. Dermat. 205:389-412, 1957.

A 48-year-old man showed exanthema in the form of petechial, erythematous, and urticarial lesions. Face, neck, chest, upper back, and upper thighs were free of lesions. Histologic findings were compatible with hemorrhagic microbid and Schönlein's purpura, respectively. There was unusual disturbance of clot retraction at the time of the outbreak of skin manifestations. Coagulation analysis showed insignificant decrease of Factor IX, inhibition of plasma retraction, and pathologic agglutination (method of J. Jürgens). Examination of thrombocytes

with the electron microscope did not reveal abnormal changes, but there was increased adhesion and concentration of thrombocytes into giant agglutinates. The formation of regular fibrin nets and the normal course of clot retraction are possibly disturbed.

HOLLANDER, Springfield, Mass.

REPORT ON THE 23D CONGRESS OF THE GERMAN DERMATOLOGIC SOCIETY. A. WIEDMAN and G. NIEBAUER, Arch. klin. u. exper. Dermat. 206:1-858 (Dec.) 1957.

This volume deals exclusively with the proceedings of the 23d Congress of the German Dermatologic Society, held in Vienna from May 24 to May 27, 1956.

The following main themes were presented. 1. Occupational dermatoses (general remarks, pathogenesis, prophylaxis, and therapy): A thorough and organized occupational fitness examination is recommended, particularly in "skin active" occupations. Protective ointments of specific nature have not given favorable results. Avoidance of the offending contactant is imperative for the prophylaxis of occupational dermatoses. 2. Radiobiologic research and its significance for the therapy of skin tumors: Improvement of the diagnosis of skin tumors may be achieved by the use of radioactive substances as well as by local and regional use of colloidal radioisotopes. Chemical radioprotection of normal tissue and increase of radiosensitivity of tumor tissue were discussed. 3. Progress in radiotherapy of skin tumors: Good results with soft x-rays in the treatment of malignant skin tumors have been obtained. Radium and x-ray therapy of hemangiomas and telangiectatic nevi were evaluated. 4. Inflammatory vascular diseases and their effect on the skin: Discussion of acute vasculitis of medium-sized and smaller arteries of muscle type (periarteritis nodosa); of arterioles, venules, and capillaries (purpura rheumatica, arteriolitis allergica, and papulose atrophiante maligne) was held. These vasculitides are considered vascular allergides. Chronic inflammatory vascular diseases and their effect on the skin (endangiitis obliterans, arteriosclerosis obliterans, ulcus hypertonicum Martorell, Raynaud's disease, and capillaropathy) were reviewed. 5. Present-day serologic syphilis diagnosis including the Nelson test: Discussion was held of the specific and classical seroreactions. 6. Histochemistry of the skin: Reviews of histochemistry of epidermis and corium and histochemistry of keratinization were presented. 7. Importance of vitamins of the skin: Discussion of chemistry of vitamins, their indications for skin therapy, and clinical results was held.

Many additional papers related to the above-named main themes were presented. Furthermore, numerous papers about clinical and experimental dermatology; serologic, bacteriologic, and mycologic research, and therapy and histopathology of the skin were read. A showing of films of rare dermatoses and a presentation of interesting clinical cases concluded the congress.

HOLLANDER, Springfield, Mass.

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Books

Non-Venereal Syphilis. By Ellis Herndon Hudson, M.D., D.T.M.&H.(Lond.), F.A.C.P. Price, $7.00. Pp. 204. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Here is an extremely interesting and informative monograph that is presented as a summary of the work conducted by the author over a thirty-year period. This is not just a textbook review of a disease but an engrossing study of the interrelationship of the host, the environment, and the parasite.

It is written in a style uncommon to the present-day rigid pattern of presenting facts. The flavor of life in the Arab community of Deir-ez-Zor, in Syria, enhances one's interest and understanding of the subject.

The theme of the monograph is to show that bejel and syphilis, as well as yaws and pinta, are but variations of one condition caused by the same organism. The group which the author calls treponematosis probably affects one hundred million persons. He attempts to show that the different manifestations "spring from the way people live, the rules and customs they live by, the social matrix in which their lives are imbedded."

There are excellent descriptions and photographs of the conditions. In addition to the clinical and social study, there are sections which review the serology and microscopic pathology of treponematosis.

Dangerous Properties of Industrial Materials. By N. Irving Sax with Leonard J. Goldwater, William B. Harris, John H. Harley, Joseph J. Fitzgerald, and Milton S. Dunn. Price, $22.50. Pp. 1467. Reinhold Publishing Corporation, 430 Park Ave., New York 22, 1957.

This is an ambitious encyclopedic reference work dealing with the hazardous properties of some 8500 materials. It is divided into sections on toxicology, ventilation, personnel protection, atmospheric pollution, industrial fire protection, storage of materials, general chemicals, radiation hazards, reactor safeguards, and allergic diseases in industry.

The material in the last three sections, which are of particular interest to dermatologists, is unusually well presented. The section on chemicals covers some one thousand pages. The book is arranged for quick reference. The various sections are thumb-indexed, and the materials covered are arranged alphabetically; for each material there is furnished information such as synonym, formula, storage, handling, toxicity, and shipping requirements. The volume contains a wealth of information which should be most useful, especially for anyone interested in industrial dermatology.

Medical Radiation Biology. By Friedrich Ellinger, M.D. Price, $20.00. Pp. 945. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This authoritative volume should serve essentially as an excellent source of reference for all those concerned with radiation and its effects. The author, undertaking an ambitious project, has systematically recorded the available information in a concise logical presentation. In the first part of the book, the fundamental principles of radiation biology are set forth. The remainder of the book is then subdivided into discussions of the biology of ionizing radiation, ultraviolet radiation, and visible and infrared radiation, with emphasis on medical significance.

Throughout, the author is careful to point out which information is well documented and which is purely theoretical and also which is derived from animal studies as distinct from human studies. There is a complete table of contents which facilitates reference and helps somewhat to make up for the lack of an index. One-fourth of the book is devoted to a comprehensive bibliography of more than five-thousand references.

The graduate student and the practitioner of dermatology, rather than the novitiate, will benefit most from this book, and for them it merits high recommendation.

Die Wirkung von Waschmitteln auf die Haut. By Helmut Stüpel and Alexander Szakall. Price, DM 26. Pp. 261, with 68 illustrations. Dr. Alfred Hüthig, Verlag, Wilckensstrasse 3, Germany, 1957.

This book consists of two parts. The first part is entitled "The Human Skin." It constitutes almost one-half of the volume and is actually a treatise on the functional biochemistry of the epidermis. It has chapters on the chemistry of keratins and theories on keratinization; on the submicroscopic (and electronmicroscopic) structure of the horny layer and of the subcorneal membrane; on water binding and water permeability of the epidermis; on its acid-base balance; on surface lipids, their replenishment, and their surface-modifying effects; on self-sterilization of the surface, etc. Dr. Szakall, a brilliant research dermatologist, became particularly well known when he succeeded in isolating and investigating in detail the subcorneal membrane, which since the 1920's was held to be the chief barrier for the exchange of materials with the outer world. Thus, it is not surprising that the review is not simply a recapitulation of findings but is written expertly from an individual and critical point of view. Some of the postulates may not remain without contradiction because of incomplete evidence, as, for instance, the claim that the free amino acids in the horny layer derive from the decomposing nuclei (as do also the keratohyalin granules) or that keratins are not fibrous proteins but are rather composed of a granular material. However, the discussion of such controversial matters makes the book even more valuable, increasing its thought-provoking qualities.

The second part of the book deals with the cutaneous effects of soaps and synthetic detergents. It is the most thorough and extensive review on the subject hitherto published. Its great virtue is its basic point of view, as it discusses the effects of wash products on biochemical and physiological functions, for instance, effects on acid-base balance, on swelling, and on colloid-chemical properties in connection with electrolyte effects. It discusses absorptive and mechanical effects and the factors of potential irritation. Excellently written chapters deal with the nature and action mechanism of soaps and detergents and with protective measures.

The literature of the whole Western world is most conscientiously considered in this monograph. The American literature on biochemistry and physiology of the skin and on effects of detergents is particularly well covered.

It is regrettable that on account of the language barrier not all research-minded dermatologists in this country will share the benefit of reading this book. Translation into English would be highly desirable.

Krankheiten der Mundschleimhaut und der Lippen (in German). Second Edition. By Dr. Hans Schuerman, Professor and Director of Dermatology, University of Würzberg, Würzberg, Germany. Price, DM 88. Pp. 524, with 325 illustrations (24 in color). Urban & Schwarzenberg, Thierschstrasse 11, Munich 26, Germany, 1958.

This book gives a very thorough and complete exposition of diseases of the oral mucosa and lips, including oral manifestations of most diseases of the skin. It is, perhaps, the best book on the subject at the present time. Among the diseases covered are the mycoses; bacterial infections, including leprosy, tuberculosis, rickettsial and virus diseases, syphilis, and leishmaniasis; the exanthemata; bullous dermatoses; erythematosquamous and pustular dermatoses; the lichenoid dermatoses; dystrophic diseases; anomalies of keratinization; contact dermatitis; deficiency diseases; the hemorrhagic diatheses; collagenous diseases; lipoidoses; diseases of the tongue, oral manifestations of systemic disease; benign and malignant tumors, and anomalies of pigmentation, among others. Each subject has a bibliography with references as late as 1957, including many articles in the American and British literature. This book will make a valuable addition to the dermatologist's library.

Atlas und Praktikum der Dermatologie und Venerologie. By W. Burckhardt. Price, DM 48. Pp. 272. Urban & Schwarzenberg, Thierschstrasse 11, Munich 26, 1958.

This new Atlas, written in German, is beautifully illustrated with faithful reproductions of color photographs. There are 99 color and 65 black-and-white photographs. The text material is concise, giving a brief word-picture of the condition, its cause, and typical effective therapy. This well-indexed volume would be an asset to the student and practitioner conversant with German.

An International Nomenclature of Yaws Lesions. By C. J. Hackett, M.D. Price, $4.00. Pp. 103. Columbia University Press, 2960 Broadway, New York 27, 1958.

This new nomenclature, recommended by the Venereal Diseases and Treponematoses Section of the World Health Organization, outmodes terms such as mother yaw, daughter yaw, ghoul hand, crab yaws, etc. The classification consists of two main groups: early yaws and late yaws. Under early yaws, there are included the various types of initial yaws: cutaneous early yaws; mucosal early yaws; early yaws of bones and joints, palms, and soles, and latent early yaws. Late yaws is also subdivided into cutaneous yaws, osseous, latent, etc. If the classification still seems a bit confused, it is only because the manifestations of the disease are such that they will not lend themselves to simplified classification.

Seventy-five of the one hundred pages consist of as fine a collection of photographic illustrations of yaws as one could wish for. The photographic collection is well worth the cost of the book.

Practical Allergy. By M. Coleman Harris, M.D., F.A.C.P., and Norman Shure, M.D., M.S., F.A.C.P. Price, $7.50. Pp. 471. F. A. Davis Company, 1914-1916 Cherry St., Philadelphia 3, 1957.

Because the "part-time allergist" is unable, for various reasons, to keep pace with the changes occurring in the practice of allergic diseases, the authors thought that to fill the void there was need for a simple text—and that this is. The writing is, in fact, at an elementary level. After a brief historical account, pertinent terms are defined, methods of skin testing and various other office techniques are described, and individual diseases are considered. Twenty pages are devoted to dermatologic allergy, and twenty, to drug reactions. The latter chapter is satisfactory, perhaps, because before publication it was reviewed by a dermatologist. The section on skin diseases could be better. For instance, in the differential diagnosis of atopic dermatitis, the authors consider among other entities, erythema multiforme, psoriasis, and even herpes simplex, which, incidentally, is said to occur usually on mucous membranes. Withal, the book does constitute an introduction to allergic diseases, written in simple terms; it expresses the established views and, in instances where questions are unsettled, all of the prevailing views. The practical features of the book should be useful.

Diseases of the External Ear. By Ben H. Senturia, M.D. Price, $8.50. Pp. 211. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1957.

The Human Ear Canal. By Eldon T. Perry, M.D. Price, $4.75. Pp. 116. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1957.

Two monographs on the same subject, one by a dermatologist and the other by an otolaryngologist, produced by the same publisher and released at the same time. What an unusual situation!

Senturia's "Diseases of the External Ear" is used as a framework to record and discuss the results of an otologist's years of research into the complex problem of external ear infections. The data substantiate and are the basis of his well-known views on factors, such as removal of skin lipids, maceration, humidity, elevated temperature, sweating, lack of cerumen, etc., all of which are considered as contributing factors to otitis externa. Pertinent literature is referred to, and his own results are well documented. Of interest is his statement that the "pendulum is swinging back"; he notes that there appears to be an increase in the incidence of superimposed otomycosis, perhaps as a result of the overuse of antibiotic-corticoid drugs. The plea is for a better understanding of underlying chemical and pathologic changes so that diseases of the ear may be prevented or more easily controlled.

The book is profusely illustrated but with photomicrographs only; there are no clinical pictures.

Perry's "The Human Ear Canal" covers the same ground but with emphasis on summarizations rather than the presentation of experimental details. The author does, however, recount his experiments in the field, assess his results, and interpret them in relation to clinical findings. It is a dermatologist's view of the ear canal presented with the thought that solution of the problem of external ear diseases will result only from cooperative efforts on the part of otologists, dermatologists, physiologists, pathologists, biochemists, and other specialists. The author's interest and training are apparently in physiologic aspects of the subject, and his presentation of material is succint, authoritative, and scholarly. He, too, refers to pertinent

literature and makes use of photomicrographs, though they are not as numerous or elaborate as in Senturia's book.

The organization of the material is orderly, the writing is of a high order, the clinical descriptions are authentic, and the treatment is sensible and based on sound principles. The book is small enough to be carried in the pocket, and it is inexpensive.

One gathers from reading these books that some diseases of the external ear are more readily recognized and better treated by dermatologists; others, by otologists, and still others require the cooperative efforts of both specialists.

Both of the books merit high recommendation.

Announcements

Psoriasis Research Award.—The Department of Dermatology, Baylor University College of Medicine, Houston, Texas, announces that Drs. J. M. Paschoud, B. Schmidli, and Walter Keller have been selected as recipients of the $1000 Award for Research in Psoriasis. The Award is given for their work that was published in the *Archiv für klinische und experimentelle Dermatologie* and in *Dermatologica* (Paschoud, J. M.; Keller, W., and Schmidli, B.: Untersuchungen über Peptidasen in der gensunden and befallenen Haut von Psoriasis kranken, *Arch. klin. u. exper. Dermat.* 203:203-216, 1956. Schmidli, B., and Paschoud, J. M.: Acides amines et polypeptides dans la peau atteinte de psoriasis, *Dermatologica* 110: 323-332, 1955). The selecting Committee was Drs. Marcus R. Caro, Edward P. Cawley, Arthur C. Curtis, Eugene M. Farber, John M. Knox, Aaron B. Lerner, and Carl T. Nelson.

This Award was established by Carol and Henry J. N. Taub in honor of their grandparents, Mr. and Mrs. J. N. Taub. The establishment of this 10-year program carried with it the hope that this Award will be the instrumentality by which a cure may be developed to alleviate one of the problems of mankind.

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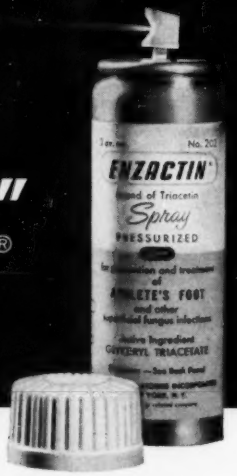

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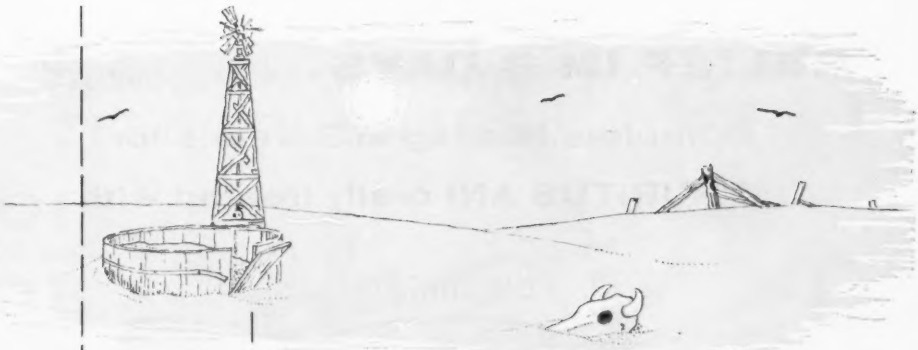

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*Miller, J. M.; Godfrey, G. C.; Ginsberg, M., and Papastrat, C. J., in Surgical Service, V. A. Hospital, Fort Howard, Maryland: Postgrad. Med. *22*:609, 1957.

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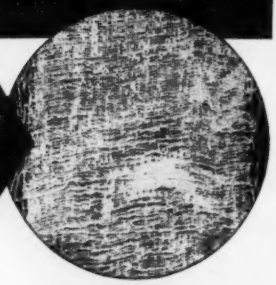

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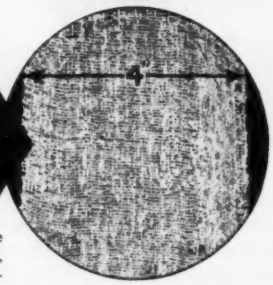

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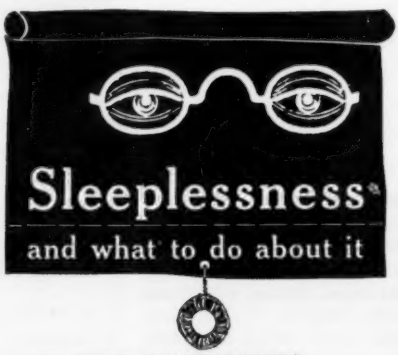

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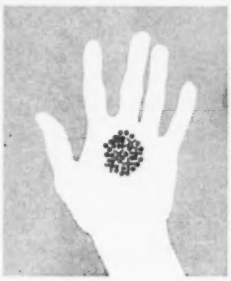

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Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off

NEW non-inflammable Gebauer's FLURO-ETHYL

(FLUORINATED-HYDROCARBON)

FLURO-ETHYL is a solution of Ethyl-Chloride and Dichlorotetrafluoro-ethane which has been demonstrated to be useful as a topical refrigerant for use in plastic surgical skin planing and as an agent to produce local anesthesia for minor surgical procedures. It contains 75% Dichlorotetrafluoro-ethane and 25% Ethyl-Chloride, and when applied topically to the skin, produces rapid refrigeration and anesthesia to the desired depths of the skin.

CLINICAL USES:

Plastic Surgical Skin Planing: In the refrigeration dermabrasion technique GEBAUER'S FLURO-ETHYL is a refrigerant of choice because it eliminates the necessity of a blower. The mixture is non-inflammable and it produces rapid anesthesia and refrigeration to the required depths of the skin. In addition, the mixture does not give the patient a feeling of suffocation if inhaled. The area to be refrigerated can easily be controlled to the desired limits.

Although this preparation is specially designed for plastic surgical skin planing, it can also be used as a local anesthetic for minor procedures such as incision of furuncles, electrocautery to small cutaneous tags, flat warts, and nevi, or the alleviation of needle pain during hypodermic injection.

HOW IT'S USED

When using GEBAUER'S FLURO-ETHYL, holding same in an inverted position, the solution is then delivered onto the skin in the form of a fine, mist-like spray, producing a degree of anesthesia by refrigeration adequate for skin planing without the use of an air blower. To obtain best results place container in cooler before using.

MANUFACTURED BY

THE GEBAUER CHEMICAL CO.

CLEVELAND 4, OHIO

INDICATED:

NEO-MAGNACORT®

neomycin and hydrocortamate

TOPICAL OINTMENT

The first water-soluble dermatologic corticoid plus neomycin, for consistently outstanding control of contact dermatitis and other inflammatory dermatoses complicated by or threatened by infection.*

In 1/2-oz. and 1/6-oz. tubes, 0.5% neomycin sulfate and 0.5% hydrocortamate hydrochloride (hydrocortisone diethylaminoacetate hydrochloride) — MAGNACORT.

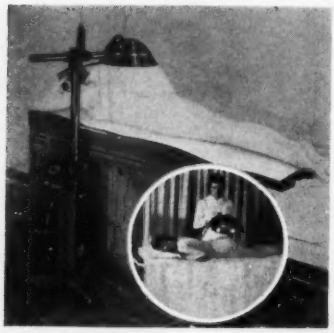
also available: MAGNACORT® Topical Ointment — in 1/2-oz. and 1/6-oz. tubes, 0.5% hydrocortamate hydrochloride (hydrocortisone diethylaminoacetate hydrochloride).

*Howell, C. M., Jr.: Am. Pract. & Digest Treat. 8:1928, 1957.

Pfizer

PFIZER LABORATORIES DIVISION, CHAS. PFIZER & CO., INC., BROOKLYN 6, NEW YORK

THE ORIGINAL FISCHERQUARTZ



Model No. 88

A MUST IN DERMATOLOGY
OVER 48,000 MANUFACTURED SINCE 1928
HIGH POWERED GERMICIDAL ULTRAVIOLET
FOR LOCAL SKIN THERAPY AND FOR
CONSTITUTIONAL EFFECTS

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Localizer

R. A. FISCHER & CO.

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normal protective cover

Normal skin has an acid pH range between 4 and 6

ACID MANTLE®

CREME or LOTION pH 4.2

Samples and literature on request

Supply:
ACID MANTLE Creme: 1 oz. tubes, 4 oz. & 16 oz. jars.
ACID MANTLE Lotion: 1 oz. and 4 oz. squeeze bottles, 1 pint bottles.

In housewives' eczema and industrial dermatitis, promptly restores and maintains the normal protective acidity of the skin. Active ingredient is aluminum acetate in specially formulated bases.

"The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalies is amply borne out..."

—Gross, P., et al.: A. M. A. Arch. Dermat. & Syph. 70:94,1954

DOME *Chemicals Inc.*
109 WEST 64 ST., NEW YORK 23, N.Y.
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effective ... in the full range of SUMMER DERMATOSES

Poison Ivy · Sunburn · Prickly Heat · Insect Bites

Humidity Rash · Chafing

2 types of AVEENO® Colloid Baths

For calming effect

AVEENO®
Colloidal Oatmeal

time-tested
widely accepted

AVEENO® Colloidal Oatmeal is available in 18 oz. and 4 lb. boxes.

For calming . . .
plus extra emolliency

AVEENO®
"OILATED"

Active Ingredients: Colloidal oatmeal concentrate, liquid petrolatum and hypo-allergenic fraction of lanolin.

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AVEENO Corporation

Pioneers in Ethically-Promoted Colloid Baths

SHEPARD'S
Cream Lotion

Contains sufficient sesame oil to lubricate without excess grease

Not occlusive

No lanolin or lanolin derivatives

Available unscented as well as scented

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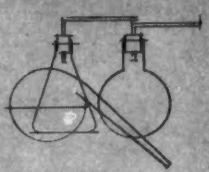
Manufacturers and Distributors of Fine Cosmetics

Coal Black is White in

Tarbonis®
cream

5% Special Coal Tar Preparation in a Vanishing Cream Base

BASIC FOR A WIDE RANGE OF COMMON DERMATOSES



TAR—basic in dermatologic therapeutics for centuries—reaches peaks in performance and acceptability in TARBONIS. An exclusive refinement process makes TARBONIS:

UNSURPASSED IN EFFECTIVENESS—Promptly relieves itching and promotes healing

COSMETICALLY ELEGANT—No messiness, no staining or odor

VERSATILE—An excellent vehicle for individualized prescription formulas

CONVENIENT—Simply apply two or three times daily. No protective dressing needed

Available at all pharmacies on prescription in jars of 2¼ oz., 8 oz. and 1 lb.

R&C **REED & CARNRICK**
Jersey City 6, New Jersey

Another First !

New SILICOTE® LIQUID SPRAY

PROTECTS SKIN AGAINST MANY IRRITANTS

Your patients can now spray on effective protection of the skin against common dry and aqueous irritants with new Silicote Liquid Spray.

Silicote Liquid Spray contains the unusually high concentration of 33 1/3% silicone (dimethicone) in a specially prepared liquid petrolatum base. It contains no water or water soluble ingredients. Silicote is the only preparation incorporating the silicones in petrolatum. Its formulation is similar to Silicote Ointment.

INDICATIONS:

Contact Dermatitis: Soaps, detergents, cosmetics.

Industrial Dermatoses: Acids, alkalies, foods, drugs, coolants, soluble cutting oils.

Surgical Drainage: Colostomy, ileostomy, draining fistulas and sinuses.

Hospital Skin Problems: Sheet burn, decubitus ulcers, incontinence.

Pediatric Skin Problems: Diaper rash, drooling, nasal drainage.

Chapping, Chafing, Intertrigo.

ADVANTAGES:

- Quick, easy application
- Prolonged, effective skin protection
- Assures patient cooperation
- Softens skin
- Non-tacky feeling
- Eliminates need for gloves
- Virtually nonocclusive, nonsensitizing, nontoxic

APPLICATION: Cleanse area. Shake dispenser before spraying and hold 10" from skin. **Hands:** Spray and rub in with hand-washing motion. Remove excess with cloth. Apply before each exposure to irritating substance. **Other Areas:** Apply routinely with each change of diaper or dressing. **Contraindications:** Do not use on weeping or infected areas.

SUPPLIED: 3 oz. aerosol containers. (Also available, Silicote Ointment.)

By the Originators of Aerosol Medications

SEND FOR LITERATURE

ARNAR-STONE LABORATORIES, INC.

SILICOTE

LIQUID SPRAY SKIN PROTECTIVE

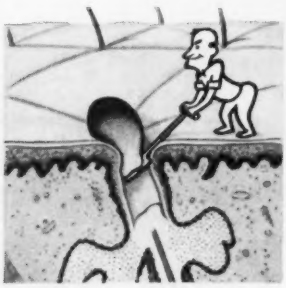
225 E. PROSPECT AVE., MT. PROSPECT, ILL.

IN ACNE

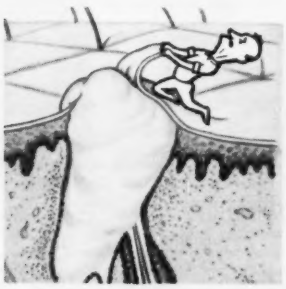
Fostex® degreases the skin and helps remove blackheads

Fostex contains a combination of surface active agents (Sebulytic*) which:

◂ Completely emulsify excess oil so that it is quickly washed off the skin.



◂ Penetrate and soften comedones, unblocking the pores and facilitating removal of sebum plugs.



Fostex dries and peels the skin

◂ The Sebulytic base of Fostex dries and promotes peeling of the skin . . . actions enhanced by the keratolytic effects of micropulverized sulfur and salicylic acid.

*(Sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, sodium dioctyl sulfosuccinate.)

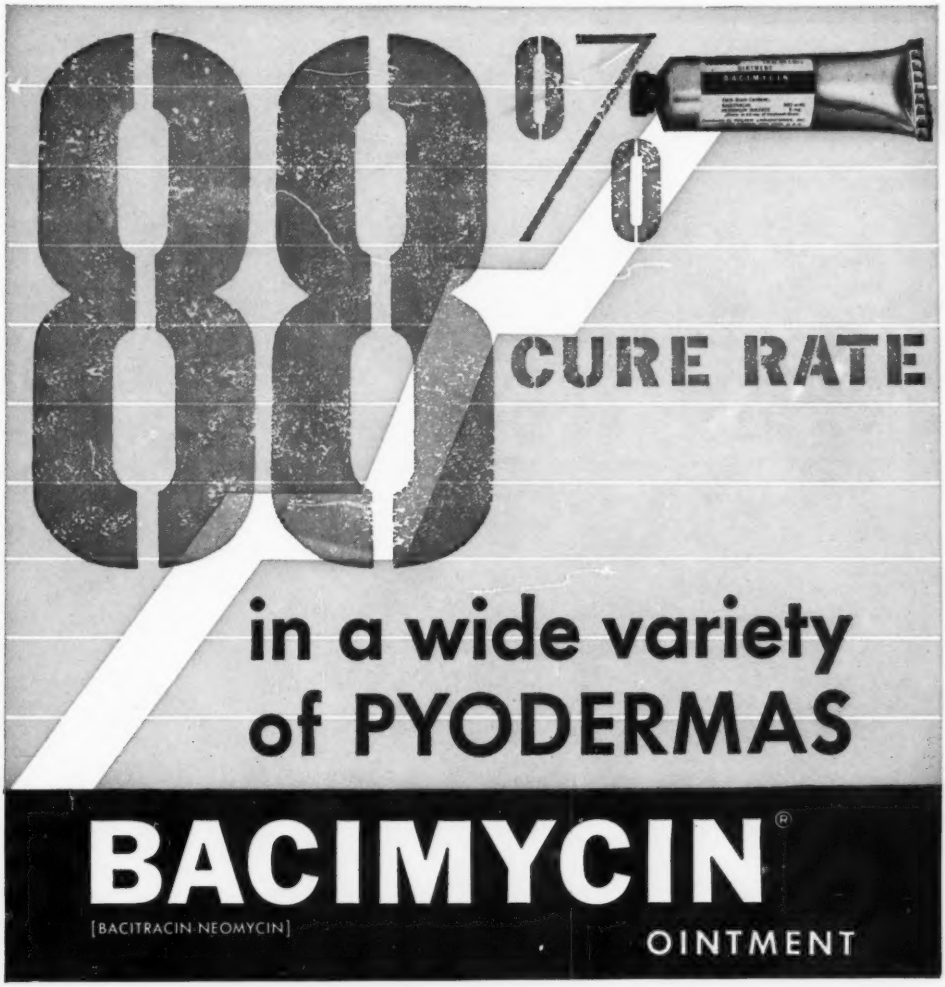
FOSTEX CREAM
for therapeutic washing of skin in the initial phase of acne treatment, when maximum degreasing and peeling are desired.

FOSTEX CAKE
for maintenance therapy to keep skin dry and substantially free of comedones.

Fostex is easy for your patients to use

◂ Patients stop using soap on affected skin areas. Instead they use Fostex for therapeutic washing of the skin. The Fostex lather is massaged into the skin for 5 minutes—then rinse and dry.

WESTWOOD *Pharmaceuticals*
Division of Foster-Milburn Co.
468 Dewitt Street • Buffalo 13, New York



a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment "... resulted in a cure rate of 88%...." Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

BACIMYCIN rarely produces sensitization or primary irritation.

Supplied in ½ oz. tubes for prescriptions; in 100 gm. jars for hospital use; in ⅛ oz. tubes for ophthalmic use. Also supplied as BACIMYCIN with Hydrocortisone, ⅛ oz. tube with applicator tip.

Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

Walker **LABORATORIES, INC.** MOUNT VERNON, NEW YORK

New!

Theradan

TRADEMARK

with Sarthionate

T. M.

Cleared up the severest dandruff with just 3 applications

...RELIEF OFTEN LASTED FOR MONTHS

Twenty months of clinical investigation on dandruff demonstrated complete clearing of scaling in all cases, usually with just three applications of easy-to-use THERADAN. Dandruff cases resistant even to resorcin, sulfur and selenium preparations usually cleared promptly and safely with new THERADAN.

Relief of scaling was found to be long-lasting—in most cases scalp stayed clear for 1 to 4 months.

HOW THERADAN ACTS

THERADAN is a therapeutic formula not a shampoo or tonic. It contains Sarthionate, our name for a distinctive new combination of a special form of sulfur and a wetting agent.

This unique solution not only clears loose dandruff, but also removes dead tissue by penetrating the outermost layers of the scalp. In mild or moderate cases of pityriasis, THERADAN is left on the scalp for one-half to one hour before shampooing. In severe cases, THERADAN is left on up to eight hours or over night.

Theradan

active ingredients

Sarthionate

bis-(lauryltrimethylammonium)-polythionate . (by weight) . 3.0%
tetradecylamine n-lauroyl sarcosine . . . . . (by weight) . 0.5%
ethyl alcohol . . . . . (by volume) . 68.86%

For more information about the clinical background of THERADAN, write to Medical Director, Dept. D-78

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